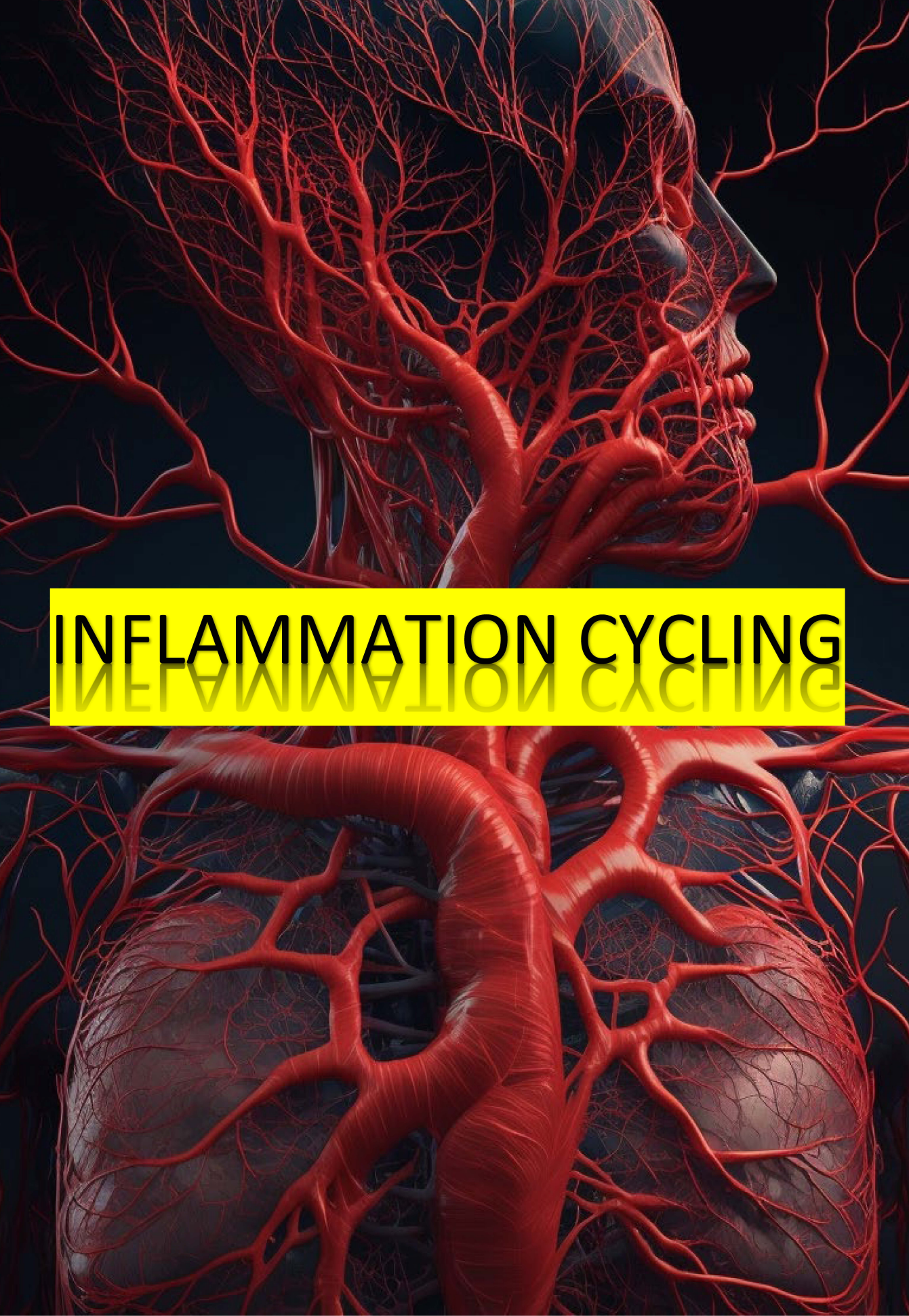
INFLAMMATION CYCLING

INFLAMMATION CYCLING

By
Dustin Sprenger

Second Edition
2025

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Forward

This is a work of curated applied human sciences research and creative correlation and like with all new knowledge the research and ideas herein should be treated with skepticism until proven true through analytical reasoning skills, and safe self-experimentation. It is my primary goal to help uninitiated readers develop into autodidacts capable of decoding, at the very least partially, breakthrough applied research—research that most practicing physicians are not aware of or too *close minded* to entertain, the type of research that gives us power over our lives.

If you have an interest in applied human sciences, and do not practice reading, or most importantly, *attempting* to read research article abstracts and full form research articles, you will continue to be slave to the Medical Industrial Complex.

In reading this book, you will encounter numerous unfamiliar terminologies that will obscure your general understanding of the assorted research I have compiled, which is why I have created suitable Overview & Glossary Sections, and have included Digital Bookmarks, do make sure to put them all to good use.

It is extremely important to understand that science is always changing and evolving, and because all research articles currently listed in this book have been formulated by human minds and are made possible through human designed tools, unintentional, and sometimes intentional errors, are liable to have occurred during their creation. Some research articles may be redacted by the time this book is published or will have their conclusions clarified making it necessary both to keep an open mind when doing your own cursory research and to find different corroborating sources to provide you all of the answers you desire. The hypotheses I posit in this book so too should be treated with skepticism, as it should always be your goal to discern what is fact, fiction, or fancy.

Because this book contains primarily abstracts, if you find a study that piques your interest, you should attempt to purchase it to gain access to a clearer picture of the study design and results. Sometimes you will be able to find research articles that exist behind a paywall but are shared openly on a different, more obscure publishing medium, if therefore you are monetarily constrained, do make good use of your search engine.

Many free full form research articles in this book have been truncated, and certain articles have had spelling or grammar errors corrected by me, to enhance readability.

In conclusion, I do not claim to be intelligent, nor a talented writer, I am quite *unremarkable*, but I do regard myself as being blessed with creativity, and having an eye for meaning (Pattern Recognition), and through these qualities this work has come into existence. Please enjoy this book and remember, no scientific complexity is beyond comprehension.

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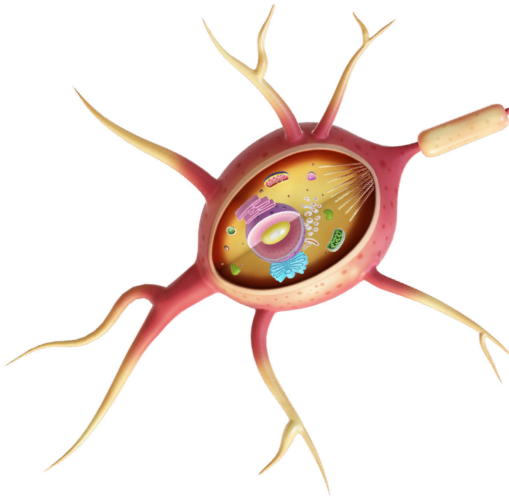

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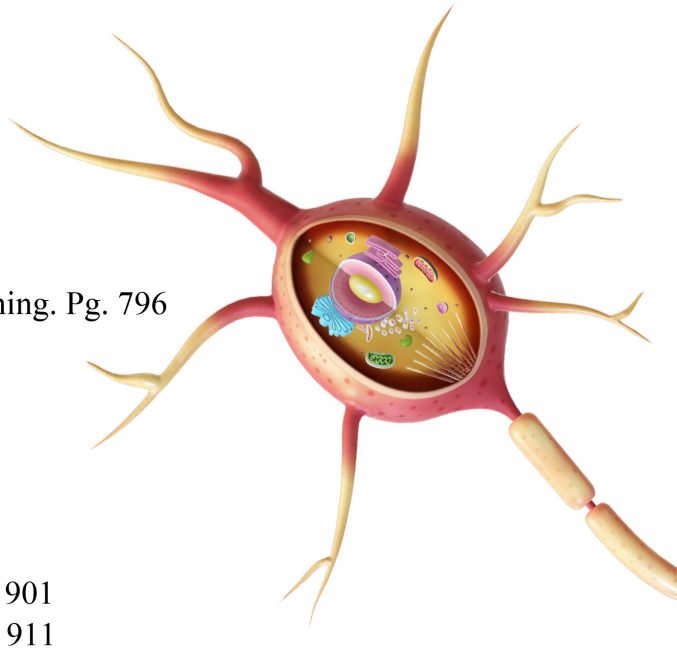
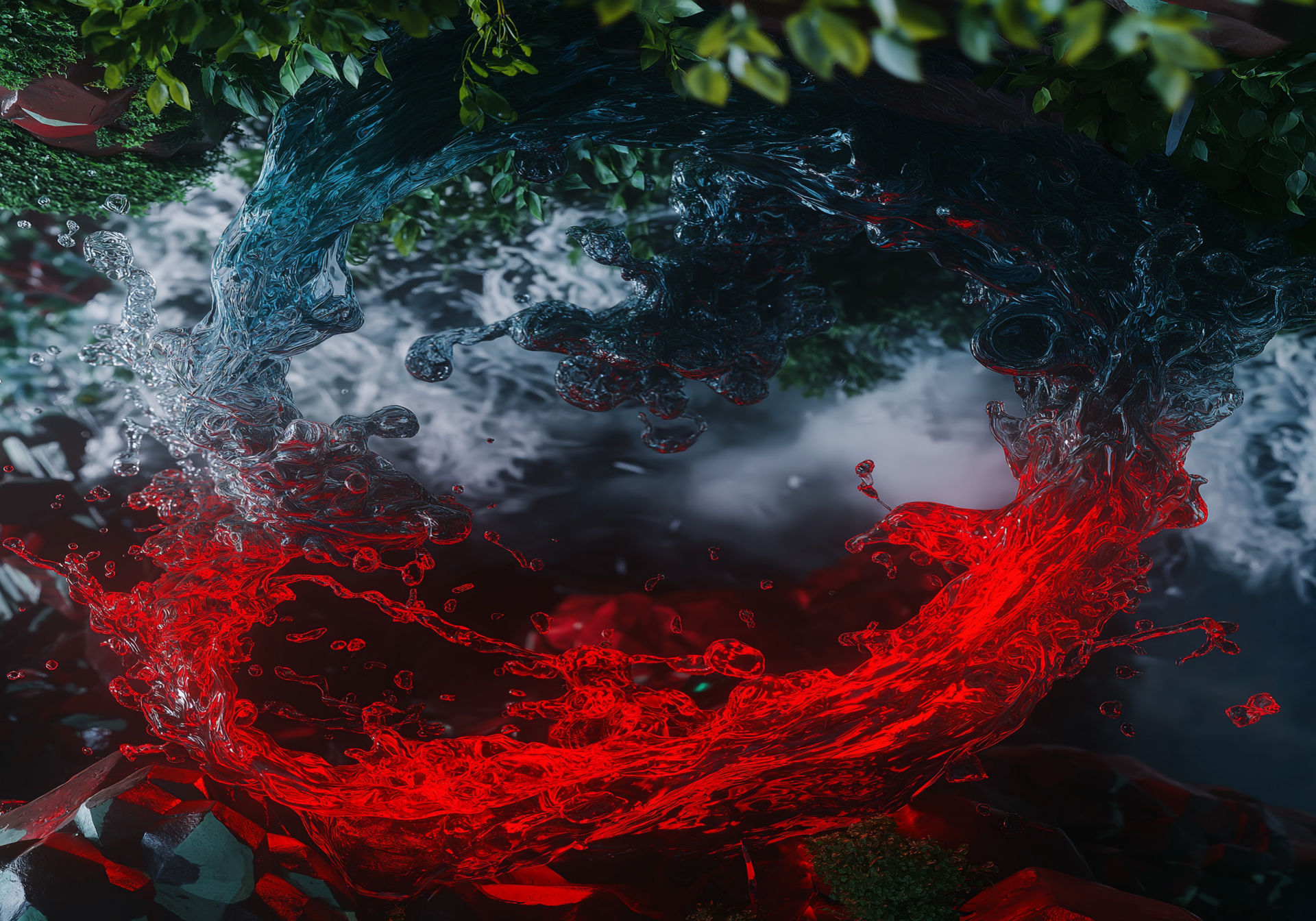




"Knowledge which is acquired under compulsion obtains no hold on the mind"
The Republic: Book 7 536 d-b: Plato

From time immemorial man has experimented with medicinal plants, using them to treat sickness and alter their consciousness. Plants are potent sources of phytochemicals capable of changing our physiology, from delaying aging, to enhancing memory, to killing cancer cells. If we understand Plant defense against herbivory, we begin to comprehend why phytochemicals exert such a potent effect on our bodies and mind, as they are in fact endogenous pesticides produced by the plants, to deter or harm herbivorous predators. Nearly all phytochemicals display the ability to kill cancer cells in research studies, yet we do not treat cancer with them for obvious and corrupt reasons, Breast Cancer will likely never be "cured", because these supposedly altruistic companies are too focused on selling merchandise.

Society continues to evolve due to scientific innovation, and we are only now understanding the precise biological effects of phytochemicals, ranging from positive to negative, we are driven ever more closely to a future without illness. To avoid the issue of cancer what follows will relate to two cycles of supplementation / modalities for the promotion of muscle growth & cognition. One cycle will be presented to you to enhance myogenesis and angiogenesis, and the other cycle to promote neurogenesis and neuroprotection.

As we move away from processed foods and animal products, and substantially increase our intake of vitamins, to follow the health trends, our systemic levels of inflammation gradually become inverted to favor an anti-inflammatory profile, we thereby reduce our muscle mass, and in certain cases our lifespan (see: Mitophagy). Although contrary to what you might expect I am not going to argue against antioxidants, in fact I argue for them, although in time-restricted usage. It is my primary goal to illustrate the benefits of both sides of the *biological coin* (Pro vs. Anti-Inflammation) and help you to better understand in which "cycle" you belong in most of the time. I am not at the time of writing / compiling this book a medical professional, nor collegiate researcher, nor am I someone who can explain properly all the intricacies of these sciences, but I can lay out my vision of humanities future, one split between two cycles: *Pro-Inflammation* and *Anti-Inflammation*.

This book is not an exhaustive study on any specific scientific discipline, its contents come from years of "web browsing" research which has arisen from my unending desire to increase my intelligence and muscle function.

I would like to truly thank all the scientists who through trial and error, and meticulous work, have created the research that I will display before you, your intellectuality and ventures into the unknown will propel humanity into the ideal future. This work is a compendium of fact and opinion, the main aim of it is to provide its readers with the knowledge needed to facilitate musculoskeletal & neurological improvement, or at the very least, to be an intriguing compilation of obscure knowledge. In this book I have attempted to provide direct name recognition to the researchers of whose research I have chosen to reference to the greatest extent.

I do not categorize the contents of this book into "chapters" as many parts are far too short to be considered as such, albeit still worthy of separation, therefore they are instead referred to as "sections". Because I enjoy the idea of free flowing information, there are dividing lines set between Sections in place of page breaks for the majority of topics in this book.

In this book I use **parentheses** to display the abstracts (concise summaries) of the research articles I have found through tens of thousands of hours browsing through the PubMed Database, I call these forays into the *abstract*—"**PubMed Journeys**".
I have decided also, due to the complexity entailed within this work, to innovatively use a diamond symbol "<>" to separate the research articles into one or more subparts to enhance readability and comprehensibility, I consider these paragraph splitting diamonds as effective visual anchors.

Myogenesis

Muscle damage primarily occurs through contraction, upon being damaged a cascade of stem cells are released and drawn into the damage muscle to form myoblasts:

1. **Pericytes** are myogenic stem cells released from our local blood vessels.
2. **Satellite Cells** are myogenic stem cells released from our muscle tissue.
3. **Adipose Tissue Derived Stem Cells** are a type of mesenchymal myogenic stem cells released from our fat cells.
4. **Mesenchymal Stem Cells** are myogenic stem cells released from our bone marrow.

Mirroring the mobilization or directly activating the production of Stem Cells, Myogenic Regulatory Factors, Cytokines, & other factors are released in damaged muscle tissue to orchestrate the process of Myogenesis. In the early stage of Myogenesis, after the dead muscle tissue has been consumed by macrophages, Satellite Cells (Stem Cells) are recruited from numerous places in the body, primarily blood vessels, and enter into the damaged muscle tissue, once there they convert into **Myoblasts (the precursors to muscle cells)**, they then proliferate & either fuse to preexisting myotubes (primary myotubes) in what I call **Early Hypertrophy,** or slowly fuse together with each other to form new myotubes in what is termed **Hyperplasia / Differentiation**. Early Hypertrophy involves the repair and formation of new Myofibrils, termed Myofibrillogenesis, these Myofibrils are the numerous contractile tube-like structures contained within a muscle fiber. Early Hypertrophy generally occurs during a period of 48-72 Hours after a workout, whereas Secondary Hypertrophy (Myogenic Differentiation / Hyperplasia) takes between **96** to **120** Hours. You will not reap the benefits of Myogenic Differentiation / Hyperplasia by training a muscle *within* its full recovery period of 4-5 Days. The majority of newly formed myotubes (nascent myotubes) end up fusing to primary (older) myotubes when damaged during high load or other intense types of

resistance training, this is best understood as the primary result of Secondary Hypertrophy.

A Hyperplasia-Differentiation based exercise protocol focused on protecting new myotubes may be properly facilitated through specialized exercise-recovery-supplementation protocols that involve most importantly, infrequent (every 144-168h) and very light "Lactic Acid Training" (Ideally 5-15% of your 1RM) to accumulate lactic acid intra-workout and avoid damaging your nascent myotubes beyond repair, in which case they will fuse to primary fibers, or possibly experience apoptosis. It is important to understand that Myogenic Differentiation and / or Hyperplasia will only occur after certain types of exercise are performed, such as Superslow training, Powerlifting, & Lactic Acid Training.

Even though your pre-existing muscle fibers may have fully regenerated 72 Hours post-workout, there is still a large amount of muscle tearing (*peeling*) between the myofibers, and we will soon understand that muscle tissue integrity is required for maximal Stem Cell release following exercise, it is unwise then to train with high loads too frequently. Furthermore, depending on the destructive nature and level of your workout, it may actually take 96 Hours for your muscles to fully heal, or compensate through Myogenic Differentiation, this is especially true for high load exercise sessions that include eccentric movements, such as many powerlifting lifts. There is also the fact that tendons regenerate slower than muscles (weeks on average). Therefore, I suggest to those who enjoy high frequency training to cycle between high load and low load training each week, every other week, or periodize their workouts on a once weekly training protocol to avoid injuries or strength plateaus.

When Inflammation is inhibited to too great a degree during early muscle regeneration, or severe muscle damage continues to occur while muscle is regenerating, as is the case with a lack of detraining / deloading, some of the damaged muscle fibers transform into collagen, and other muscle fibers break down into smaller fibers (dedifferentiation), resulting in a loss in muscle cross sectional area (size) & potentially losses to muscle force output. While it is possible to facilitate both hypertrophy and hyperplasia by training a muscle only once per week by carefully modulating inflammation (Rapid Inflammation Cycling), you will miss out an opportunity to magnify the angiogenic, hypertrophic, technical (motor memory), and neuromuscular synaptic functional improvements that accompany resistance training.

It must be clarified that not all exercise results in equivalent muscle damage, beyond weight (light, moderate, heavy, etc.), there is tempo, there is range of motion, and there is volume. Full ROM exercises, and Superslow exercises will always require greater recovery periods, whereas traditional concentric Isometrics performed in a controlled manner will always result in the least amount of muscle damage, followed by explosive training. Eccentric contraction leads to greater muscle damage because of increased myofiber peeling, leading to greater $Ca2+$ release, which promotes cytokine production, that of which remains high in muscle tissue for longer amounts of time (72h). It is commonly suggested that the increased and prolonged inflammation associated with eccentric exercise is bad, that it damages muscle tissue, that antioxidants can be used to quell this inflammation and protect muscle tissue from damage, but this is simply untrue,

as inflammation most often parallels muscle damage, meaning that this prolonged inflammatory state is necessary towards hypertrophy and optimal muscle regeneration.

To further explain myogenesis: Hypertrophy requires an activated immune system (Pro-Inflammation: $CD4^+$ T-cells: The first cascade of cytokine release), whereas Hyperplasia in many ways requires a suppression in immune activity (Anti-Inflammation: The secondary cascade of cytokine release) and extended recovery. All forms of wound healing, whether Muscle, Skin, or Tendon, require increased Pro-Inflammation factors to mobilize the immune system to repair and build new tissue.
We will learn that Pro-Inflammation factors such as IL-6, Cyclooxygenase-2, Tumor Necrosis Factor Alpha, & Nuclear Factor Kappa Beta are nearly always associated with Hypertrophy (early wound healing), although these factors inhibit Hyperplasia if left unchecked.
The natural progression of myogenesis is: 0-48h / 0-72h (Day 1-2 / Day 1-3) of Inflammation: NF-κB, Angiogenesis, IL-6 Increase, COX2 Increase, TNF-A Increase, Capase-3 Increase, Reactive Oxygen Species Increase, followed by 72h (Day 3-5) of Anti-Inflammation: IL-10 Increase, NF-κB Suppression, COX2 Suppression, TNF-A Suppression. Post-exercise muscle inflammation increases are dependent on exercise intensity, the harder you train, the longer period of inflammation there will be within your muscles, especially for eccentric exercise (72h), but the general timespan inflammatory infiltration is 48 Hours. If one is to engage in Hyperthermia Therapy immediately post-exercise, and in the following days, I believe this pro-inflammatory process is accelerated to completion at 24-48h.

0-48h Myogenic Proliferation:
IL-6, TNF-a, NF-kB, COX2

24-124h Myogenic Differentation:
IL-10, Suppressed IL-6 / TNF-a /
NF-kB / COX2

It is interesting to note that Hypertrophy can occur simultaneously alongside muscle breakdown, such that you may continue to grow a muscle while training it every day, or twice a day, but this is not sustainable when the damage exceeds the body's repair ability, which I believe must involve the loss of exercise-induced angiogenesis, macrophage populations, and a genetically predetermined wound healing rate limitation. An example

of this would be to perform 200 Repetitions per day of 1LB dumbbell biceps curls, because the damage to the muscle would be so minute, you could perform this workout every day and still experience growth, although you would be accumulating muscle damage over time and would still require a detraining period of 48-72h every week or two. Conversely, if you performed 200 Repetitions of 15LB dumbbell biceps curls per day, you may experience transient growth, but you would soon plateau and eventually regress as you begin to progressively destroy more and more secondary myotubes.

It is vital to mention I do not suggest strength trainers or power trainers follow the 72h Rule of Recovery, considering there is far more complexity to exercise recovery than merely hypertrophy. There are tendons to consider, and joints, and ligaments, and genetic factors that will prevent optimal recovery between high load resistance training sessions every 72h, especially in natural athletes, who are often fooled by *enhanced athletes* into following protocols designed for and by those who have an unfair myogenic advantage, therefore it is my suggestion to maintain 96h recovery periods between all high load or high intensity exercise sessions, although you can still train a muscle in this recovery period, even the day after, with very low loads, such as with warmup percentages or aerobics.

Understand that Primary Myotube Hypertrophy will not be negatively impacted by training a muscle during its recovery periods of 0-72h, depending on the loads lifted, and volume of the workout. Going for a one hour low intensity bicycle ride the day after squatting maximal weights is not going to substantially decrease the growth of your legs but squatting heavy for two or three days in a row will, after you pass the threshold benefit of overtraining, although you will be perturbing, or inhibiting myogenic differentiation, which if repeated frequently will result in lessened future growth. It is far better idea for a natural athlete to train more often, with low-moderate loads, than to train less often with high-max loads, as inflammation can only bring you so far if you do not possess a myriad of drugs and supplements to boost stem cell proliferation post-exercise, leading to wasted potential.

Muscle Protein Synthesis is a process that describes the influx of Amino Acids in and out of muscle tissue, wherein they activate myogenic transcription factors or myogenic genes. Most Amino Acids compete with one another for entry into muscle cells, making it necessary to consume complete proteins (all Essential Aminos), although there are two amino acids that are of the greatest importance to athletic performance.

Interestingly, some Satellite Cells are capable of transforming into adipocytes, depending on the concentration of Insulin, and Dexamethasone (Prescription Cortisol derivative) during activity. Furthermore, Slow Twitch muscle-derived satellite cells are more prone to undergo adipogenic transformation, clearly due to intramuscular lipids being used as a major source of fuel during periods of extreme starvation or endurance exercise.[0]

Addendum A: To further explain everyday training, I believe any percentage lifted at or below 15% your 1RM, may be used, if the volume is not high, and the tempo is concentric, or “Regular-speed”, with the hypertrophy occurring being subtle and long

lasting, at the cost of maximal force generation, that is to say, CNS adaptation. Training with Warmup percentages everyday will also accelerate slow twitch muscle fiber regeneration, if the weight is light enough of course (Aerobics). What effect very low load (likely resistance band) explosive training would have on the regeneration of fast twitch muscle fibers is as of yet unknown:

"<>Introduction: As skeletal muscle mass recovery after extensive injury is improved by contractile activity, we explored whether concomitant exercise accelerates recovery of the contractile and metabolic phenotypes after muscle injury.
<>Methods: After notexin-induced degeneration of a soleus muscle, Wistar rats were assigned to active (running exercise) or sedentary groups. Myosin heavy chains (MHC), metabolic enzymes, and calcineurin were studied during muscle regeneration at different time points.
<>Results: The mature MHC profile recovered earlier in active rats (21 days after injury) than in sedentary rats (42 days). Calcineurin was higher in the active degenerated than in the sedentary degenerated muscles at day 14. Citrate synthase and total lactate dehydrogenase (LDH) activity decreased after injury and were similarly recovered in both active and sedentary groups at 14 or 42 days, respectively. H-LDH isozyme activity recovered earlier in the active rats.
<>Conclusions: Exercise improved recovery of the slow/oxidative phenotype after soleus muscle injury."[0.1]

Addendum B: Increasing muscular inflammation will benefit physical strength (slow twitch fiber growth), but not physical power. Inflammation is not a negative process for fast twitch athletes, as you can always isolate your glycolytic fibers through specialized training if necessary, and muscle damage still requires a certain level of inflammation to regenerate efficiently. Absolute Strength (Muscle Power) is far more dependent on CNS strength, Neuromuscular Junction Synaptic Density, and Motor Memory strength, meaning that no amount of pro-inflammatory supplementation will make you into a world class Powerlifter, but experimenting with extended Detraining periods of 96-Hours or longer, alongside Superslow Training, specifically Eccentric Training, may very well be the keys to the maximization of muscle power.

"<>Introduction: Skeletal muscles are characterized by their unique ability to regenerate. Injury of a so-called fast-twitch muscle, extensor digitorum longus (EDL), results in efficient regeneration and reconstruction of the functional tissue. In contrast, slow-twitch muscle (soleus) fails to properly reconstruct and develops fibrosis. This study focuses on soleus and EDL muscle regeneration and associated inflammation.
<>Methods: We determined differences in the activity of neutrophils and M1 and M2 macrophages using flow cytometry and differences in the levels of proinflammatory cytokines using Western blotting and immunolocalization at different times after muscle injury.

<>Results: Soleus muscle repair is accompanied by increased and prolonged inflammation, as compared to EDL. The proinflammatory cytokine profile is different in the soleus and ED muscles.
<>Conclusions: Muscle repair efficiency differs by muscle fiber type. The inflammatory response affects the repair efficiency of slow- and fast-twitch muscles."[0.2]

Myogenic Points to memorize:

- Vascular Endothelial Growth Factor (VEGF), a protein molecule you will discover soon, is essential for both the early and late stages of myogenesis, although research is limited on its relation to Hyperplasia.
- "Complete Myogenesis" is to be defined as describing the full process of Myogenesis (Hypertrophy and Hyperplasia). Some compounds such as L-Carnitine promote Complete Myogenesis.
- Muscle size does not always equate to absolute strength for the reason of Sarcomere-Costamere dynamics, Neuromuscular Junctions, and the CNS.
- Very few human beings train as infrequently as hyperplasia requires, we primarily experience the benefits of Pro-Inflammatory processes, that is early wound regeneration, and its benefits on muscle size and strength.
- It is also improbable that a focus on Hyperplasia will benefit a natural athlete without dozens of years of carefully programmed low load training, requiring an extreme form of self-control & patience, and squandered potential.

[A] Repeated for effect: Understand that hypertrophy cannot occur alongside hyperplasia. In the later section on Stretching, we see that chronically damaging muscles every 72 Hours (followed by daily stretching for a short period) without detraining or deloading results in a transition from hypertrophy to hyperplasia-like muscle regeneration. The processes generally do not occur simultaneously, not when rest days between workouts are adequate, or when inflammation levels in the body are not suppressed, or excessive, but after damage to muscle tissue exceeds a certain threshold, over some unknown period of time, a portion of hypertrophied fibers will in all likelihood break down in human scenarios. Whether this is beneficial or not is up for debate. Therefore, for the purposes of hypertrophy alone, there is no reason to combine Anti-Inflammation supplements or modalities with high intensity exercise (damaging exercise: high load).[1]x[506.1]

[B] Adipose Tissue derived stem cells play an integral role in the age-old positive effect of bodybuilder "bulking" cycles. Having a higher content of bodily adipose tissue does promote muscle growth, depending on the variables of overall health, and the training style and exercise frequency pursued, such that the more adipose tissue a person has, the more often they should train, to mitigate the deleterious consequences of excessive inflammation, and intramuscular lipids, and most importantly to protect their overtaxed hearts from the toll of providing oxygen to the essential but often pathogenic adipocytes.
"<>MSCs from adipose tissue as well as bone marrow have been shown to bear myogenic potential, which makes them ideal candidate stem cells for skeletal muscle

tissue engineering applications. When compared to reconstructive procedures using autograft tissues, MSC therapy offers the potential of reducing or even eliminating donor-site morbidity. This review gives a comprehensive overview of the use of MSCs in in vitro muscle generation and in vivo muscle regeneration."[2]

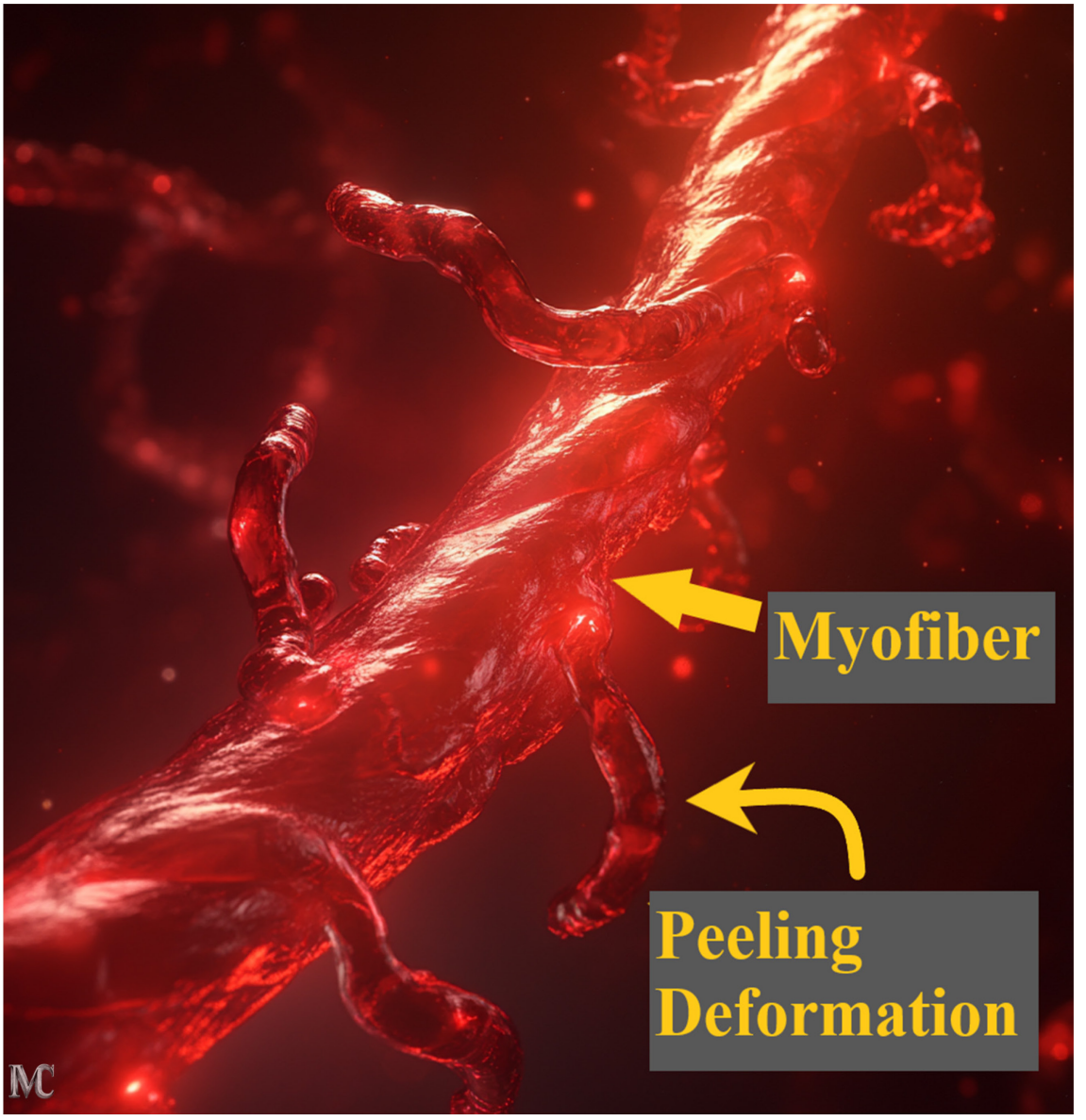
Skeletal Muscle Mechanotransduction

The scientific process of resistance training, wherein mechanical signals stimulate the release of biochemical signals in muscle tissue after deformation (damage) during and after contraction.

[A] "<>Cell mechanotransduction, the ability to detect physical forces and convert them into a series of biochemical events, is important for a wide range of physiological processes. Cells express an array of mechanosensors transducing physical forces into intracellular signaling cascades, including ion channels. Ion channels that can be directly activated by mechanical cues are known as mechanically activated (MA), or stretch-activated (SA), channels. In response to repeated exposures to mechanical stimulation in the form of resistance training, enhanced protein synthesis and fiber hypertrophy are elicited in skeletal muscle, whereas a lack of mechanical stimuli due to inactivity/mechanical unloading leads to reduced muscle protein synthesis and fiber atrophy."[2.1]

[B] Muscle damage occurs during contraction because of **Peeling Deformation** (damage), and not as I had once believed, "friction" deformation. One should not confuse a "Myofiber", with a "Myotube", as a Myofiber is a mature (developed) and active Myotube, which contains Myonuclei, and numerous Myofibrils. This novel knowledge of Peeling Deformation may be the answer to why Overtraining always results in Myogenic plateaus, where at some point during strenuous high frequency training muscle tissue reaches its *Peeling Threshold*, where it can no longer maintain its integrity, or connectiveness, resulting in either dedifferentiation, muscle fibrosis, or muscle apoptosis.

"<>The distinction between shear and tensile stress is important. Tensile loading and tensile strength are straightforward, familiar concepts. Ropes are loaded in tension and derive their strength from the tensile strength of the constituent fibers. That rope derives its flexibility from the ability of those stiff fibers to slide relative to each other. The arrangement of rope fibers results in a structure that is strong in tension because of the strength of individual fibers, but weak in shear because of the lack of connection between adjacent fibers. The connective tissue and adhesions that anchor a cell are relatively strong in shear, but relatively weak in tension, making myofibers easier to separate by peeling than by sliding"[2.1.0]



[C] Myofibers are composed of Primary and Secondary Myotubes. Primary Myotubes are of large diameter, they are primarily the myofibers that develop from birth. Secondary Myotubes fuse to Primary Myotubes during the later stages of Myogenesis. Think of the Primary Myotube as being a Barbell, with the Secondary Myotubes being a thick foam wrapped around the barbell. With this knowledge in mind, we begin to understand that overtraining is the result of Secondary Myotubes being “peeled” off during contraction from Primary Myotubes, and how with an insufficient supply of Myogenic Stem Cells after injury comes a regression in Myofiber diameter i.e. Secondary Myofibers. Furthermore, this information explains why bodybuilders generally lose most of their muscle hypertrophy following cessation of anabolic steroids, as they have grown

primarily their Secondary Myotubes, which are more sensitive to atrophy factors and apoptosis, yet their myofibers retain their myonuclei,

"<>Developing muscles contain at least two types of myoblasts. Early myoblasts are the first myoblast to form and are the only myoblasts present during primary myotube formation. By the time secondary myotube formation begins, early myoblasts are rare and late myoblasts are common. The late myoblasts have been postulated to give rise to secondary myotubes. While this is generally accepted, it is unclear whether late myoblasts also contribute to the growth of primary myotubes. One study has produced evidence that myoblasts present during secondary myogenesis selectively fuse with each other or with secondary myotubes, but not with primary myotubes.
<>However, the sizes of primary myotubes increase during secondary myotube formation. We have therefore re-examined the question of whether primary myotubes absorb new nuclei during secondary myotube formation. Pregnant rats were given a single intraperitoneal injection of 5 mg of 5-bromodeoxyuridine (BrdU) on one embryonic day (from E13 to E19) and their embryos removed on E20. The brominated-nuclei were labelled with an antibody to BrdU and the myotubes were marked with anti-myosin antibodies. Double labelled sections from the soleus, tibialis anterior, and extensor digitorum longus muscles were examined with a confocal microscope. The numbers and locations of labelled nuclear profiles in primary and secondary myotubes were counted and recorded.
<>The results show: (1) that primary myotubes absorb nuclei at all stages of development, including the period of secondary myotube formation; (2) that in the early stages of secondary myotube formation, more myoblasts fuse with primary than secondary myotubes whereas this situation is reversed by the end of secondary myotube formation; and (3) that the nuclei added to primary and secondary myotubes during the early stages of their formation are located within the middle of E20 muscles. The nuclei added to growing myotubes are preferentially located at the ends of the muscles."[2.1.1]

Myonuclei

The nuclei of skeletal muscle, located between the cell membrane and myofiber. Muscles also contain the nuclei of fibroblasts, stem cells, and endothelial cells, these are collectively called the Myonuclei. Myonuclei are in effect the "brains" of a muscle fiber, controlling its memory, size, and strength.

Satellite Cells do not only promote early muscle regeneration, but they form Myonuclei and accrue over time in myofibers. They are necessary for muscle hypertrophy but not always muscle regeneration, depending on the type of exercise performed and its intensity (destructive potential).

One should not confuse Myonuclei for Neuromuscular Junctions, those of which work together with motor memories stored within the brain to exert complex motor pathway patterns of force (contraction: exercise), See: Motor Units, Muscle Contraction, & Neuromuscular Junctions.

"<>With exercise in adults, satellite cells activate, often proliferate, and may fuse to muscle fibers depending on the stimulus. Historically, the fusion of satellite cells in response to mechanical stimuli in adult muscle is thought to be for the purposes of: (1) mediating the repair of focal damage to the muscle fiber, and/or (2) myonuclear addition to maintain the so-called "myonuclear domain" (i.e., a given myonucleus in the muscle fiber syncytium can only transcriptionally govern a finite jurisdiction) in response to hypertrophic growth (reviewed previously by our laboratory).
<>Satellite cells could accelerate muscle fiber repair processes given their involvement after muscle membrane re-sealing–; however, the findings of McCarthy et al. indicate that muscle fiber damage associated with robust short-term overload-induced hypertrophy is repairable without the explicit need for satellite cells, assuming that the few remaining satellite cells do not compensate in some way or some other cell type does not adopt the damage repair role of satellite cells.
<>Even after 8 weeks of overload without satellite cells, muscle fiber function normalized to fiber size is not compromised. If membrane damage is not catastrophic, cell autonomous membrane repair mechanisms intrinsic to muscle fibers seem sufficient under strenuous mechanical load. Conversely, excessively damaging protocols involving forced intense running in the absence of satellite cell fusion results in significant muscle impairments. Thus, the degree and cause of damage during load-induced hypertrophy, as well as the specific hypertrophic stimulus, likely determines the necessity of satellite cells for successful hypertrophic adaptation.[2.2]

[A] High Intensity Training (Example: Sprinting Exercise: High Volume, Low-Load Explosives) facilitates great increases in muscle Myonuclei.

"<>Skeletal muscle adapts to external stimuli such as increased work. Muscle progenitors (MPs) control muscle repair due to severe damage, but the role of MP fusion and associated myonuclear accretion during exercise are unclear. While we previously demonstrated that MP fusion is required for growth using a supra-physiological model, questions remained about the need for myonuclear accrual during muscle adaptation in a physiological setting.
<>Here, we developed an 8 week high-intensity interval training (HIIT) protocol and assessed the importance of MP fusion. In 8 month-old mice, HIIT led to progressive myonuclear accretion throughout the protocol, and functional muscle hypertrophy.
<>Abrogation of MP fusion at the onset of HIIT resulted in exercise intolerance and fibrosis. In contrast, ablation of MP fusion 4 weeks into HIIT, preserved exercise tolerance but attenuated hypertrophy. We conclude that myonuclear accretion is required

for different facets of exercise-induced adaptive responses, impacting both muscle repair and hypertrophic growth."[3]

[A2] "<>Introduction: The myonuclear domain theory postulates that myonuclei are added to muscle fibers when increases in fiber cross-sectional area (i.e., hypertrophy) are ≥26%. However, recent studies have reported increased myonuclear content with lower levels (e.g., 12%) of muscle fiber hypertrophy. Purpose: This study aimed to determine whether a muscle fiber hypertrophy "threshold" is required to drive the addition of new myonuclei to existing muscle fibers.
<>Methods: Studies of resistance training endurance training with or without nutrient (i.e., protein) supplementation and steroid administration with measures of muscle fiber hypertrophy and myonuclei number as primary or secondary outcomes were considered. Twenty-seven studies incorporating 62 treatment groups and 903 subjects fulfilled the inclusion criteria and were included in the analyses. Results: Muscle fiber hypertrophy of ≤10% induces increases in myonuclear content, although a significantly higher number of myonuclei are observed when muscle hypertrophy is ~22%. Additional analyses showed that age, sex, and muscle fiber type do not influence muscle fiber hypertrophy or myonuclei addition.
<>Conclusions: Although a more consistent myonuclei addition occurs when muscle fiber hypertrophy is >22%, our results challenge the concept of a muscle hypertrophy threshold as significant myonuclei addition occurs with lower muscle hypertrophy (i.e., <10%)."[4]

[B] Hypertrophied muscle fibers might have a cap on their growth based on their Myonuclei, pointing out the potential benefits of detraining & protocols focused on lactic acid accumulation, or hyperplasia.

"<>Mammalian cells exhibit remarkable diversity in cell size, but the factors that regulate establishment and maintenance of these sizes remain poorly understood. This is especially true for skeletal muscle, comprised of syncytial myofibers that each accrue hundreds of nuclei during development.
<>Here, we directly explore the assumed causal relationship between multinucleation and establishment of normal size through titration of myonuclear numbers during mouse neonatal development. Three independent mouse models, where myonuclear numbers were reduced by 75, 55, or 25%, led to the discovery that myonuclei possess a reserve capacity to support larger functional cytoplasmic volumes in developing myofibers.

<>Surprisingly, the results revealed an inverse relationship between nuclei numbers and reserve capacity. We propose that as myonuclear numbers increase, the range of transcriptional return on a per nuclear basis in myofibers diminishes, which accounts for both the absolute reliance developing myofibers have on nuclear accrual to establish size, and the limits of adaptability in adult skeletal muscle."[5]

[C] An argument for high frequency training in those with high testosterone (androgens) and cytokines and an argument against high frequency training in those with low testosterone or pro-inflammatory cytokines.

"<>More than one-fourth of our cohort (26%) did not experience measurable hypertrophy. The complete lack of growth was associated with no domain expansion (i.e., protein accretion) and no detectable satellite cell activation. We therefore suspect failure or impaired sensitivity of a common, upstream mechanotransduction process that initiates both protein synthesis and satellite cell activation. Transmembrane protein complexes associated with dystrophin and the integrins have been considered in this regard. Whether these subjects are truly nonresponders or actually delayed responders requires further study.
<>The possibility certainly exists that this cohort would experience hypertrophy with additional weeks of training. Studies with prolonged recovery periods between bouts (2 days/wk loading) have often resulted in more robust hypertrophy of myofibers than 3 days/wk training for both men and women, particularly in older adults. It therefore stands to reason that some subjects who failed to experience hypertrophy in this study may better respond to extended recovery time between bouts and/or additional weeks of training, and both factors should be considered in future evaluations of the mechanisms driving resistance training-mediated hypertrophy among humans."[6]

[C2] Androgens are myogenic through enhancement of satellite cell production.

"<>Aim: To investigate how suppression of endogenous testosterone during an 8-week strength training period influences the activity of satellite cells and myonuclei.
<>Methods: Twenty-two moderately trained young men participated in this randomized, placebo-controlled, and double-blinded intervention study. The participants were randomized to treatment with a GnRH analogue, goserelin (n = 12), which suppresses testosterone or placebo (n = 10) for 12 weeks. The strength training period of 8 weeks started after 4 weeks of treatment and included exercises for all major muscles. Biopsies were obtained from the mid-portion of the vastus lateralis muscle.
<>Results: Testosterone resting level in goserelin was 10-20 times lower compared with placebo, and the training-induced increase in the level of testosterone was abolished in goserelin. Training increased satellite cells number in type II fibres by 20% in placebo and by 52% in goserelin ($P < 0.01$), whereas the myonuclear number significantly increased by 12% in type II fibres in placebo and remained unchanged in goserelin ($P < 0.05$). No changes in satellite cells and myonuclei were seen in type I fibres in either group. Data from the microarray analysis indicated that low testosterone affects the bone morphogenetic proteins signalling, which might regulate proliferation vs. differentiation of satellite cells.
<>Conclusion: Eight weeks of strength training enhances the myonuclear number in type II fibres, and this is largely blocked by the suppression of testosterone. The data indicate

that low testosterone levels could reduce the differentiation of satellite cells to myonuclei via the bone morphogenetic proteins signaling pathway, resulting in reduced increases in lean leg mass."[7]

[D] Myonuclei formed during training, which parallel muscle size and strength, are not affected by muscle atrophy factors or aging. This study highlights the necessity of resistance training in early life, to future-proof oneself from later life sarcopenia.

"<>Effects of previous strength training can be long-lived, even after prolonged subsequent inactivity, and retraining is facilitated by a previous training episode. Traditionally, such "muscle memory" has been attributed to neural factors in the absence of any identified local memory mechanism in the muscle tissue. We have used in vivo imaging techniques to study live myonuclei belonging to distinct muscle fibers and observe that new myonuclei are added before any major increase in size during overload. The old and newly acquired nuclei are retained during severe atrophy caused by subsequent denervation lasting for a considerable period of the animal's lifespan. The myonuclei seem to be protected from the high apoptotic activity found in inactive muscle tissue.
<>A hypertrophy episode leading to a lasting elevated number of myonuclei retarded disuse atrophy, and the nuclei could serve as a cell biological substrate for such memory. Because the ability to create myonuclei is impaired in the elderly, individuals may benefit from strength training at an early age, and because anabolic steroids facilitate more myonuclei, nuclear permanency may also have implications for exclusion periods after a doping offense."[8]

[E] Myonuclei numbers in muscle fibers depend solely on hypertrophy.

"<>Adult skeletal muscle fiber is a symplast multinuclear structure developed in ontogenesis by the fusion of the myoblasts (muscle progenitor cells). The nuclei of a muscle fiber (myonuclei) are those located at the periphery of fiber in the space between myofibrils and sarcolemma. In theory, a mass change in skeletal muscle during exercise or unloading may be associated with the altered myonuclear number, ratio of the transcription, and translation and proteolysis rates.
<>Here we review the literature data related to the phenomenology and hypothetical mechanisms of the myonuclear number alterations during enhanced or reduced muscle contractile activity. In many cases (during severe muscle and systemic diseases and gravitational unloading), muscle atrophy is accompanied by a reduction in the amount of myonuclei. Such reduction is usually explained by the development of myonuclear apoptosis. A myonuclear number increase may be provided only by the satellite cell nuclei incorporation via cell fusion with the adjacent myofiber. It is believed that it is these cells which supply fiber with additional nuclei, providing postnatal growth, work hypertrophy, and repair processes."[9] [Truncated]

[F] On Muscle Memory.

“<>Memory is a process in which information is encoded, stored, and retrieved. For vertebrates, the modern view has been that it occurs only in the brain. This review describes a cellular memory in skeletal muscle in which hypertrophy is 'remembered' such that a fibre that has previously been large, but subsequently lost its mass, can regain mass faster than naive fibres. A new cell biological model based on the literature, with the most reliable methods for identifying myonuclei, can explain this phenomenon. According to this model, previously untrained fibres recruit myonuclei from activated satellite cells before hypertrophic growth. Fibres that have acquired a higher number of myonuclei grow faster when subjected to overload exercise, thus the nuclei represent a functionally important 'memory' of previous strength.”[10]

[F2] “<>It is unknown if adult human skeletal muscle has an epigenetic memory of earlier encounters with growth. We report, for the first time in humans, genome-wide DNA methylation (850,000 CpGs) and gene expression analysis after muscle hypertrophy (loading), return of muscle mass to baseline (unloading), followed by later hypertrophy (reloading). We discovered increased frequency of hypomethylation across the genome after reloading (18,816 CpGs) versus earlier loading (9,153 CpG sites).
<>We also identified AXIN1, GRIK2, CAMK4, TRAF1 as hypomethylated genes with enhanced expression after loading that maintained their hypomethylated status even during unloading where muscle mass returned to control levels, indicating a memory of these genes methylation signatures following earlier hypertrophy. Further, UBR5, RPL35a, HEG1, PLA2G16, SETD3 displayed hypomethylation and enhanced gene expression following loading, and demonstrated the largest increases in hypomethylation, gene expression and muscle mass after later reloading, indicating an epigenetic memory in these genes.
<>Finally, genes; GRIK2, TRAF1, BICC1, STAG1 were epigenetically sensitive to acute exercise demonstrating hypomethylation after a single bout of resistance exercise that was maintained 22 weeks later with the largest increase in gene expression and muscle mass after reloading. Overall, we identify an important epigenetic role for a number of largely unstudied genes in muscle hypertrophy/memory.“[11]

[F3] Anabolic Steroid use, as expected, results in permanent increases to myonuclei density, which is not lost during cessation. This means firstly, aside from bone density and neuronal growth differences, that trans women competing against biological women will never be myogenically fair, even after endogenous testosterone production has been suppressed, and secondly, that past steroid users who go “off cycle” and yet continue to lift impressive weights are not in fact very impressive at all. Anabolic Steroids do not cause a transient increase to strength, power, explosivity, and endurance, they cause a permanent increase to these metrics. This does not mean however that it is necessarily easy to reach prior states of Myonuclei Memory.

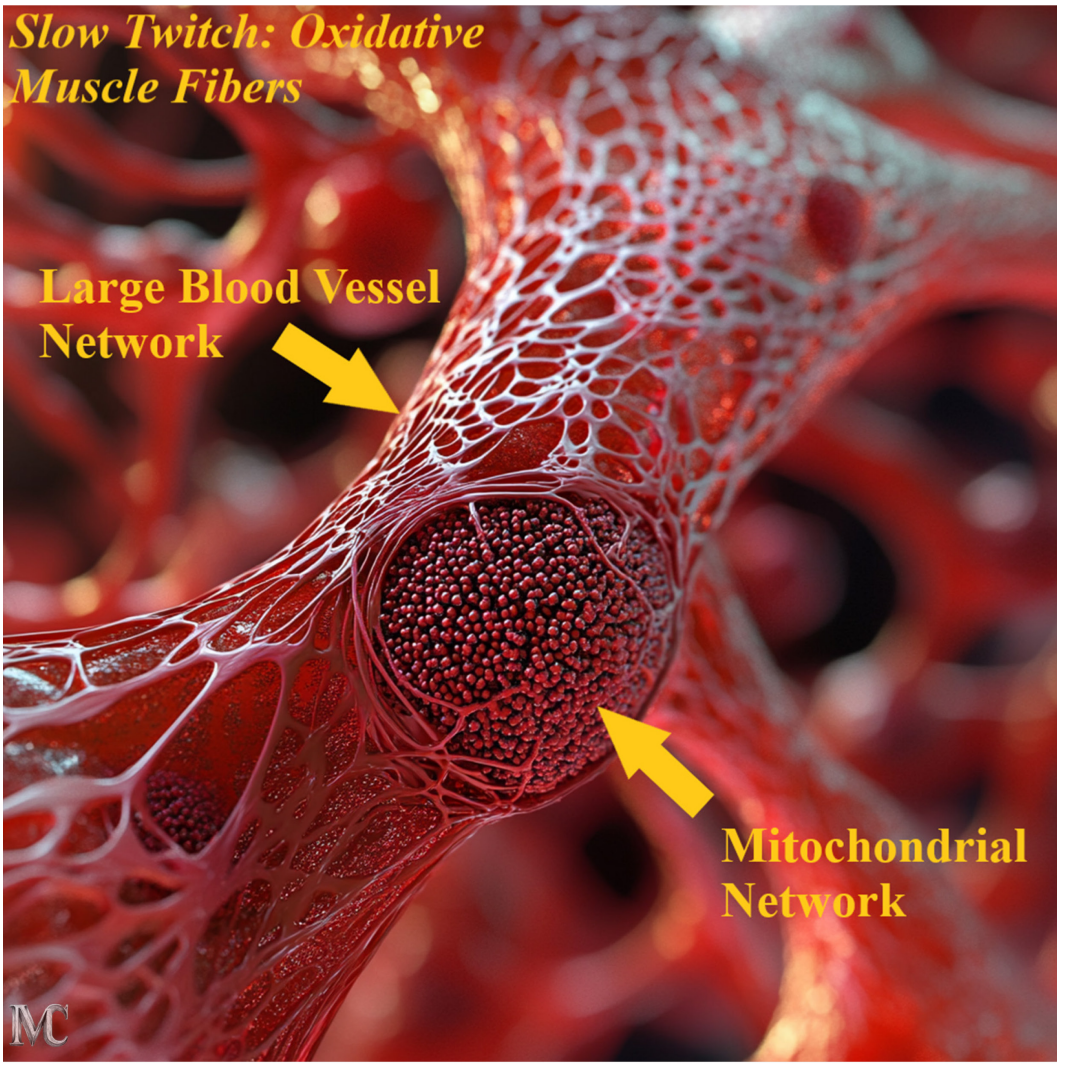
"<>Abstract: No information exists on the long-lasting effects of supraphysiological anabolic androgenic steroids (AASs) usage on the myocellular properties of human skeletal muscle in previous AAS users.
<>Objective: We hypothesized that former AAS users would demonstrate smaller myonuclei domains (ie, higher myonuclei density) than matched controls.
<>Methods: A community-based cross-sectional study in men aged 18-50 years engaged in recreational strength training. Muscle biopsies were obtained from the m. vastus lateralis. Immunofluorescence analyses were performed to quantify myonuclei density and myofiber size.
<>Results: Twenty-five males were included: 8 current and 7 previous AAS users and 10 controls. Median (25th-75th percentiles) accumulated duration of AAS use was 174 (101-206) and 140 (24-260) weeks in current and former AAS users, respectively (P = .482). Geometric mean (95% CI) elapsed duration since AAS cessation was 4.0 (1.2; 12.7) years among former AAS users. Type II muscle fibers in former AAS users displayed higher myonuclei density and DNA to cytoplasm ratio than controls, corresponding to smaller myonuclei domains (P = .013). Longer accumulated AAS use (weeks, log2) was associated with smaller myonuclei domains in previous AAS users: beta-coefficient (95% CI) −94 (−169; −18), P = .024. Type I fibers in current AAS users exhibited a higher amount of satellite cells per myofiber (P = .031) than controls.
<>Conclusion: Muscle fibers in former AAS users demonstrated persistently higher myonuclei density and DNA to cytoplasm ratio 4 years after AAS cessation suggestive of enhanced retraining capacity."[11.1]

Muscle Fiber Types

Simplified there are Type I Fibers (Slow Twitch: Oxidative: Containing Mitochondria and numerous blood vessels) and Type II Fibers (Fast Twitch: Glycolytic: Containing Glucose and less numerous blood vessels). The fast twitch fibers are responsible for classical muscle power-explosiveness, whereas the slow are responsible for muscle strength-endurance. Mitochondria are often only found in slow twitch fibers, but there are hybrid fibers containing both.

The Myosin Heavy Chain (MHC) motor proteins found in the deepest parts of Myofibrils convert ATP into mechanical force; they also direct muscle fiber transformation and activate muscle responses like cytokine release from exercise-induced damage. Muscle Fiber type is substantially altered by exercise type & diet (specifically fatty acids, See: Pro-Inflammation Dietary Fats: Lauric Acid). Aging is associated with predominately atrophied Fast Twitch muscle fibers, leading to a higher probability of insulin resistance due to less glucose disposal availability. Strength training preferentially enhances Type IIA fiber growth, which are Fast Twitch Oxidative Fibers (containing mitochondria). Slow Twitch fibers are associated with far greater bDNF release post-

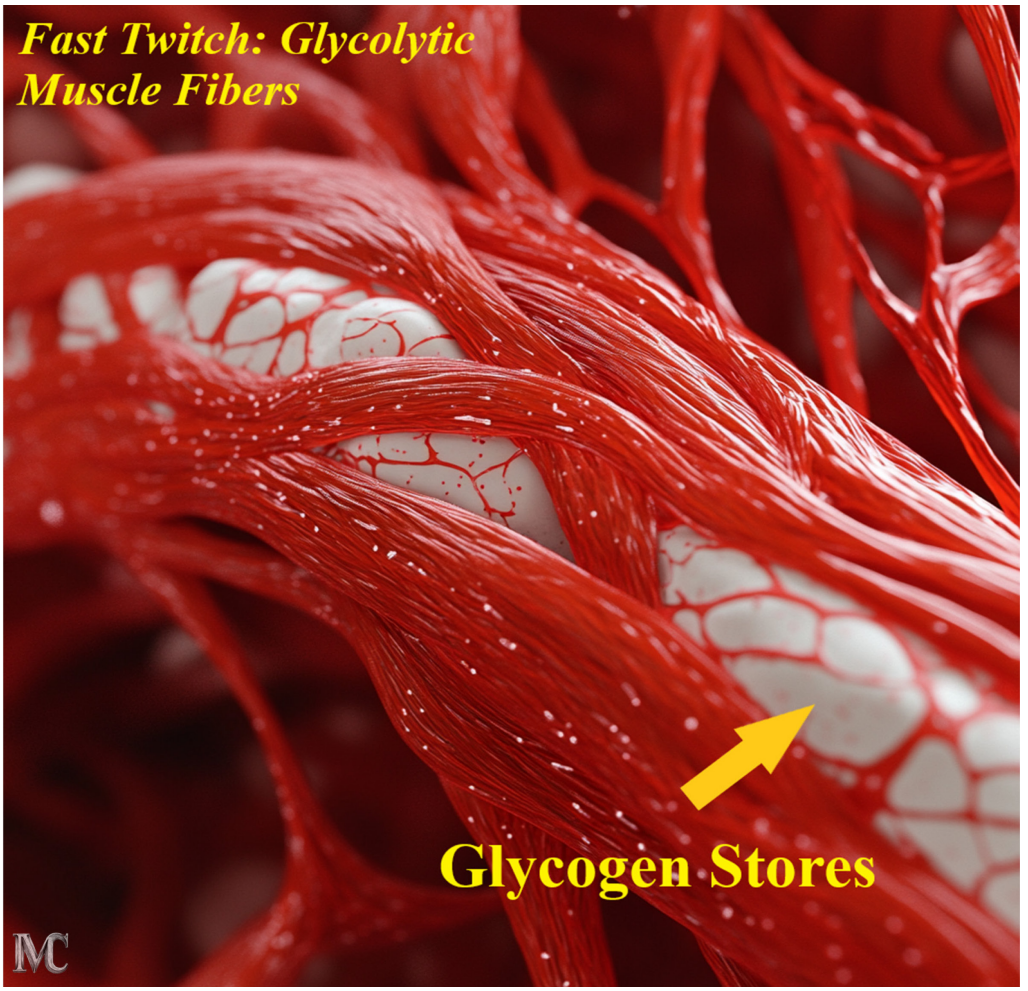
exercise, especially lactate-inducing exercise (See: Myokines), thus Endurance Training, Lactic Acid producing Resistance Training or Cardiovascular Training, and general Aerobics are far more beneficial for the brain than traditional Strength Training.



Because Fast Twitch fibers tend to contain *less dense blood vessel networks*, they recover slower than Slow Twitch fibers, and also likely because of their size differences (they are 1-1.5x larger on average) they require a greater amount of stem cells to regenerate, this means that the maintenance and growth of Fast Twitch fibers is much more difficult in the natural athletes myogenic milieu due to differences in stem cell populations, making light load training a necessity for these individuals. Although fast twitch fibers are generally associated with muscle force and absolute strength, slow twitch fibers do contribute to maximal exertions in muscle force. Detraining promotes Fast Twitch fiber growth for the reasons of reduced metabolic stress, greater glucose availability, and

improved regenerative potential due to the aforementioned size differences of muscle fiber types.

I believe Fast Twitch fiber growth benefits to a much greater extent from Myogenic Differentiation, whereas Slow Twitch fiber growth benefits from an early or maintained post-exercise intramuscular rise in pro-inflammatory factors. That is not to say Pro-Inflammation = Slow Twitch, and Anti-Inflammation = Fast Twitch, but that it may be a far more intelligent idea to separate Slow and Fast Twitch fiber growth periods by Inflammation, to simplify the sciences.



"<>Skeletal muscle fibers can be classified based on two criteria: 1) how fast do fibers contract relative to others, and 2) how do fibers regenerate ATP. Using these criteria, there are three main types of skeletal muscle fibers recognized. Slow oxidative (SO) fibers contract relatively slowly and use aerobic respiration (oxygen and glucose) to produce ATP. Fast oxidative (FO) fibers have relatively fast contractions and primarily use aerobic respiration to generate ATP. Lastly, fast glycolytic (FG) fibers have relatively fast contractions and primarily use anaerobic glycolysis. Most skeletal muscles in a human body contain all three types, although in varying proportions. The speed of

contraction is dependent on how quickly myosin's ATPase hydrolyzes ATP to produce cross-bridge action. Fast fibers hydrolyze ATP approximately twice as rapidly as slow fibers, resulting in much quicker cross-bridge cycling (which pulls the thin filaments toward the center of the sarcomeres at a faster rate). The primary metabolic pathway used by a muscle fiber determines whether the fiber is classified as oxidative or glycolytic. If a fiber primarily produces ATP through aerobic pathways, then it is classified as oxidative. More ATP can be produced during each metabolic cycle, making the fiber more resistant to fatigue. Glycolytic fibers primarily create ATP through anaerobic glycolysis, which produces less ATP per cycle. As a result, glycolytic fibers fatigue at a quicker rate.
<>Slow oxidative fibers have structural elements that maximize their ability to generate ATP through aerobic metabolism. These fibers contain many more mitochondria than the glycolytic fibers, as aerobic metabolism, which uses oxygen (O2) in the metabolic pathway, occurs in the mitochondria. This allows slow oxidative fibers to contract for longer periods because of the large amount of ATP they can produce, but they have a relatively small diameter and thus do not produce a large amount of tension. In addition to increased numbers of mitochondria, slow oxidative fibers are extensively supplied with blood capillaries to supply O2 from the bloodstream. They also possess myoglobin, an O2-binding molecule similar to hemoglobin in the red blood cells. The myoglobin stores some of the needed O2 within the fibers themselves and is partially responsible for giving oxidative fibers a dark red color. The ability of slow oxidative fibers to function for long periods without fatiguing makes them useful in maintaining posture, producing isometric contractions, and stabilizing bones and joints. Because they do not produce high tension, they are not used for powerful, fast movements that require high amounts of energy and rapid cross-bridge cycling."[12]

[A] An argument for detraining to facilitate fast twitch fiber growth. Detraining has the capacity to promote slow to fast twitch fiber conversion.

"<>Muscle fibers are composed of functional units called sarcomeres. Within each sarcomere are the myofibrillar proteins myosin (the thick filament) and actin (the thin filament). The interaction of these 2 myofibrillar proteins allows muscles to contract. Several classification techniques differentiate fibers based on different myosin structures (isoforms) or physiologic capabilities. The myosin molecule is composed of 6 polypeptides: 2 heavy chains and 4 light chains (2 regulatory and 2 alkali). A regulatory and an alkali light chain are associated with each of the heavy chains. The heavy chains contain the myosin heads that interact with actin and allow muscle to contract. The myosin heavy chain in the head region also contains an adenosine triphosphate (ATP) binding site and serves as the enzyme (adenosinetriphosphatase [ATPase]) for hydrolyzing ATP into adenosine diphosphate (ADP) and inorganic phosphate (PI), which provides the energy necessary for muscle contraction. The thin filament is made of actin and 2 regulatory proteins, troponin and tropomyosin.
<>When the muscle fiber receives a stimulus in the form of an action potential, Ca2+ is released from the sarcoplasmic reticulum. The calcium then binds to troponin and, through tropomyosin, exposes a myosin binding site on the actin molecule.4 In the

presence of ATP, the myosin head binds to actin and pulls the thin filament along the thick filament, allowing the sarcomere to shorten. As long as Ca2+ and ATP are present, the myosin heads will attach to the actin molecules, pull the actin, release, and reattach. This process is known as cross-bridge cycling. The speed at which cross-bridge cycling can occur is limited predominantly by the rate that the ATPase of the myosin head can hydrolyze ATP".
"<>Changes in the muscle fiber types are also responsible for some of the loss of function associated with deconditioning. Experiments in animals involving hind-limb suspension, which unloads hind-limb muscles, and observations of humans and rats following microgravity exposure during spaceflight have demonstrated a shift from slow to fast muscle fiber types. In addition, numerous studies on animals and humans with SCI have demonstrated a shift from slow to fast fibers. In humans, detraining (ie, a decrease in muscle use from a previously high activity level) has been shown to lead to the same slow to fast conversion, with shifts from MHCIIa to MHCIIx/d and possibly MHCI to MHCIIa. There is also a concomitant decrease in the enzymes associated with aerobic-oxidative metabolism. In summary, decreased use of skeletal muscle can lead to a conversion of muscle fiber types in the slow to fast direction."[13]

[A2] Hybrid muscle fiber types.

"<>The overall mechanical and metabolic performance of the muscles is a consequence of the heterogeneous mosaic composition of different muscle fiber types that make up the muscle. One basis of this heterogeneity is the expression of specific myosin isoforms. There are eleven of these are expressed in adult mammalian muscles, but some are specific to one muscle. The most common isoforms are MHCIb, MHCIIa, MHCIIb, and MHCIId.
<>Immunohistochemistry reveals that some muscle fibers are "pure" types that express only a single myosin heavy chain (MHC) isoform, whereas other muscle fibers contain two or more isoforms and are "hybrids." How can this be? Recall that each muscle fiber contains many nuclei, typically located at the periphery of the cell near the sarcolemma, (the) nucleus controls a volume of cytoplasm or surface of the fiber called its "nuclear domain." A separate population of nuclei congregates near the neuromuscular junction. During transitions between fiber types, it is possible that some of these nuclei receive different signals than others, and therefore transcribe different genes for the expression of myosin. In this way, hybrid muscle fiber types arise. The existence of hybrid muscle fibers allows a more continuous gradation between muscle types."[14]

[B] Muscle fiber type in relation to its size.

"Fiber areas vary between different fiber types. Type IIB fibers have the fastest rate of contraction and are also the largest in terms of CSA (cross sectional area). Within an individual muscle, average fiber sizes increase in the order type I < IIA < IID < IIB, with considerable overlap in the size ranges of each fiber type."[15]

[C] Powerlifters have more Type IIA fibers.

"<>In the present study, a primary difference between the PL and CON was the considerable difference in the relative area occupied by each major fiber type. The net result is a much greater potential contribution from IIA fibers, which made up almost 52% of the total cross-sectional area for the PL, and a smaller contribution from IIB fibers, which made up slightly more than 1% of the cross-sectional area. The CON subjects exhibited over 12% of the IIB area, in-dicative of a large portion of fibers seldom recruited. The relative area of type I fibers was comparable for PL and CON, again suggesting that the most important functional contribution for power lifting is the fiber-type distribution and size within the type II fiber population. The combination of fiber type and area exhibited by the PL may be an important factor in powerlifting performance. A large percentage of IIB area is not critical to successful power lifting performance.
<>These data suggest that long-term training for powerlifting does not result in a decrease in type I fiber area because of a type I to type IIA shift. It is possible that the active lifestyle of the CON subjects may have contributed to larger than expected areas for their fibers."[16]

[D] Endurance exercise clearly causes a transformation of Type II fibers into Type I fibers.

"<>Background: Researchers employing a variety of training methods have demonstrated a fast-to-slow fibre transformation in animal skeletal muscle. The observation as to whether this occurs in exercise trained humans is limited and equivocal.
<>Experimental design: to examine this issue, skeletal muscle from seven subjects who had participated in a decade or more of high intensity aerobic training (DT) and six nontrained (NT) subjects was obtained by muscle biopsy from the vastus lateralis muscle (VL) and subjected to a modified myofibrillar ATPase technique to identify muscle fibre types. Muscle tissue was histochemically treated by exposure to an alkaline preincubation (pH 9.9), an acid preincubation (pH 4.3 or 4.6) and the formate-KCI preincubation buffer (pH 4.54), previously employed in animal studies.
<>Results: The percentage of type I fibres in DT was 70.9% vs 37.7% in NT ($p<0.01$), while the type IIa fibres in DT (25.3%) was much lower ($p<0.01$) than NT (51.8%). Surprisingly, type IIa fibres in the DT group displayed lesser oxidative staining intensity ($p<0.01$) than type IIa fibres from the NT group. Mean cross-sectional area of type I fibres for DT (6233.9+/-1421.7 microm2) was greater ($p<0.05$) than either type I (5746.8+/-1135.2 microm2) or II (5693.5+/-1214.6 microm2) from NT.
<>Conclusions: The results revealed that endurance training may promote a transition from type II to type I muscle fibre types and occurs at the expense of the type II fibre population."[17]

Cytokines

Succinctly explained:

"<>Cytokines are small cell-signaling proteins that are secreted by numerous cell types. Cytokines have very prominent roles in regulating both the innate and adaptive immune systems, and in the process of inflammation. Cytokines function by acting on the cells that secrete them (autocrine) or on nearby cells (paracrine).
<>Importantly, most cytokines function in their local microenvironment, rather than in a systemic manner. Cytokines bind to specific cell surface receptors, thereby activating intracellular signaling cascades that involve phosphorylation events that ultimately result in gene transcription. Because of their involvement in immune and inflammatory responses, cytokines hold promise as therapeutic targets."[18]

The Pro-Inflammatory proteins MAPK's (p38, ERK1/2, JNK) & Nuclear Factor Kappa B (NF-kB) activate cytokine production post-injury or when stimulated. The Cytokines I am familiar with include Interleukin 1-17, Tumor necrosis factor, Interferon, & Transforming Growth Factor. Nearly all cytokines promote myogenesis (wound healing), *but in chronic concentrations they are toxic to brain/muscle cells*. IL-6 is associated with early wound regeneration, and IL-10 is associated with late stage wound regeneration, but both are capable of causing muscle atrophy and toxicity depending on concentration and time.

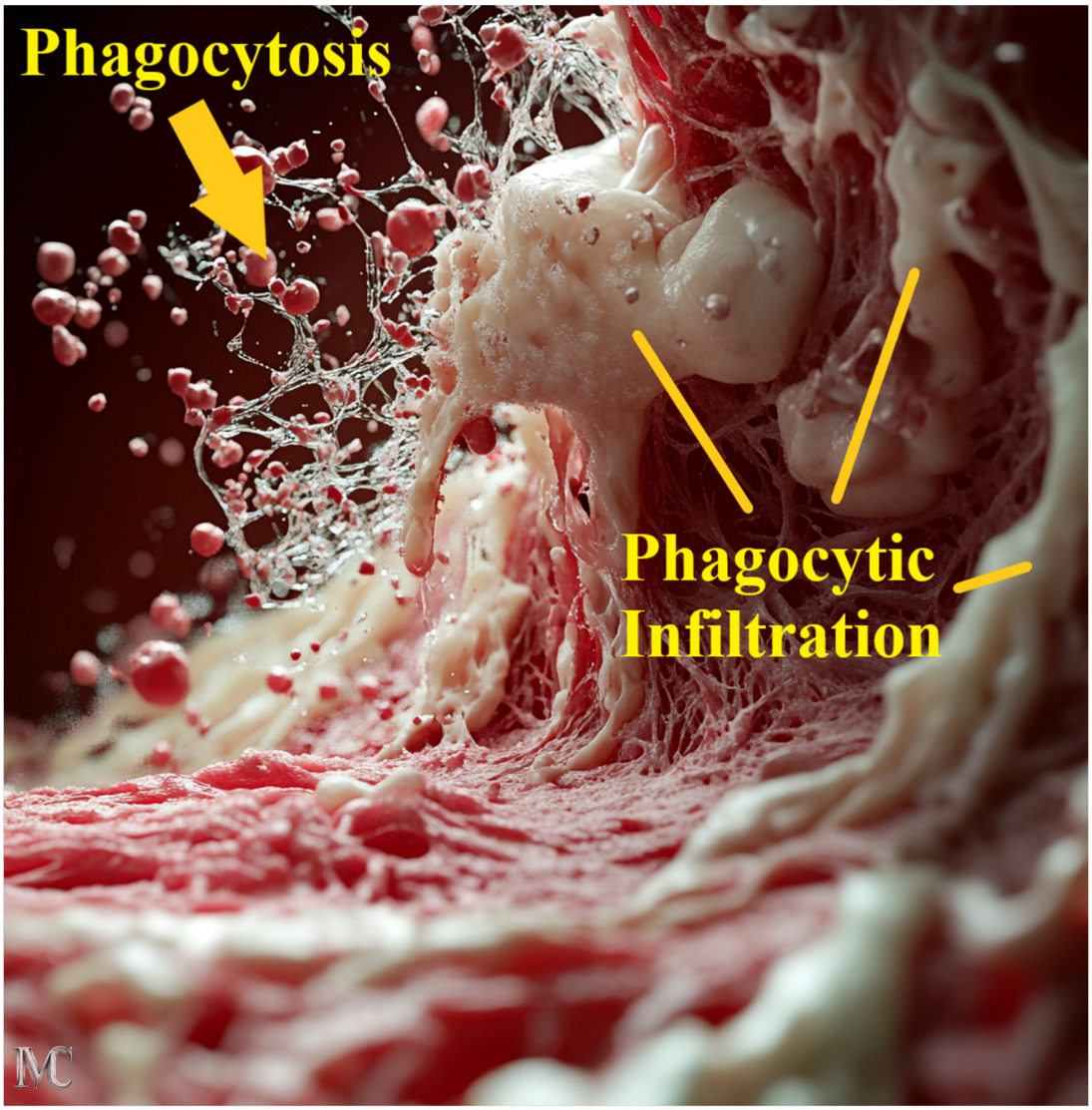
Macrophages

These white blood cells play an integral part in muscle regeneration; they are associated with the early & late stages of muscle regeneration. Without adequate macrophage activity you will halt the process of hypertrophy and retain dead muscle tissue within your muscles post-exercise due to insufficient phagocytosis, wherein specialized cells enter into damaged muscle tissue and consume dead tissue, thereby making cellular space for regenerative and adaptive myogenic growth.

Cytokines are essential for optimal stem cell/macrophage activity post-injury, especially CD8 T Cells [C]. There are two polarizations of Macrophages during myogenesis, the first is M1 which is the early Pro-Inflammatory immune state of regeneration, the second is M2 which is the late Anti-Inflammatory immune state of regeneration. M1/M2 Macrophages release cytokines in response to injury.

It is quite clear that the M1 macrophage phenotype is capable of promoting muscle fibrosis or atrophy, as we all know the dangers of unfettered inflammation, but interestingly, the M2 (Anti-Inflammatory) macrophage phenotype if overactive during early muscle regeneration, will suppress or inhibit myogenesis, or cause outright muscle fibrosis. The study below describes the anti-fibrotic effect and necessity of Nitric Oxide

produced by M1 macrophages in skeletal muscles and discusses the complications of uncontrolled M2 polarization in a common form of muscular dystrophy.



Quelling inflammation is not a magic cure to muscle atrophy, and if you use too many IL-10 boosting antioxidant chemicals, or other chemicals that Polarize the body towards an M2 phase, while physically training strenuously, and often, you may end up losing muscle tissue, as Early Hypertrophy is a very important process for preexisting muscle tissue maintenance and preservation. Of course, if you purposefully avoid damaging the muscles too greatly, by training with low volume, or ideally, low loads, a chronically active M2 Polarization will in theory not harm your regenerative potential, this being due to a faster entry into Myogenic Differentiation.

“<>For example, neutrophils and activated M1 macrophages invading the muscle are observed around 4 weeks of age in the mdx mice, a genetic mouse model for Duchenne muscular dystrophy (DMD). In contrast, the infiltration of M2 macrophages also occurs at the early stages of inflammation in DMD. This differs from acute muscle injury, which M2 macrophages usually predominate at later stages of inflammation. The invasion of M2 macrophages at the early stages of inflammation inhibits production of NO by M1 macrophages and greatly decreases M1 macrophage lysis of muscle cells. The repression of fibrosis by NO is therefore attenuated. It leads to pathological fibrosis which occurs at the late stage of muscle regeneration in chronic muscle disorders.
<>M2 macrophages also participate in activation of cytotoxic T cells that are then able to promote muscle damage through perforin-mediated processes. In addition, M2 macrophages induce an increase of anti-inflammatory cytokines such as IL-4, IL-10 and IL-13, which can induce the activation of eosinophils that promotes muscle fibrosis through major basic protein-1–mediated processes.”[18.1]

[A] “<>Inflammation is usually considered as harmful; however, it is also necessary for tissue recovery after injury. Macrophages exert immune and nonimmune functions throughout this process. During skeletal muscle regeneration, they mount an inflammatory response while exerting trophic roles on muscle and mesenchymal stem cells. Proinflammatory macrophages shift to being anti-inflammatory, triggering the resolution of inflammation. Studies have highlighted that during this shift, a crosstalk ensues, integrating cues for resolution, efferocytosis, cellular metabolism, and signaling pathways. During the restorative phase, macrophages dampen inflammation while promoting stem cell differentiation, angiogenesis, and matrix remodeling. Since blunting the inflammatory phase can be detrimental for muscle regeneration, we suggest that rather than fighting inflammation, it should be allowed to operate and resolve, thus allowing for tissue recovery.”[19]

[B] "<>Anti-inflammatory strategies are often used to reduce muscle pain and soreness that can result from high-intensity muscular activity. However, studies indicate that components of the acute inflammatory response may be required for muscle repair and growth. The hypothesis of this study was that cyclooxygenase (COX)-2 activity is required for compensatory hypertrophy of skeletal muscle. We used the synergist ablation model of skeletal muscle hypertrophy, along with the specific COX-2 inhibitor NS-398, to investigate the role of COX-2 in overload-induced muscle growth in mice. COX-2 was expressed in plantaris muscles during compensatory hypertrophy and was localized mainly in or near muscle cell nuclei. Treatment with NS-398 blunted the increases in mass and protein content in overloaded muscles compared with vehicle-treated controls.
<>Additionally, the COX-2 inhibitor decreased activity of the urokinase type plasminogen activator, macrophage accumulation, and cell proliferation, all of which are required for hypertrophy after synergist ablation. Expression of insulin-like growth factor-1 and phosphorylation of Akt, mammalian target of rapamycin, and p70S6K were increased following synergist ablation, but were not affected by NS-398. Additionally, expression of atrogin-1 was reduced during hypertrophy, but was also not affected by

NS-398. These results demonstrate that COX-2 activity is required for skeletal muscle hypertrophy, possibly through facilitation of extracellular protease activity, macrophage accumulation, and cell proliferation."[20]

[C] "<>Inflammatory microenvironments play a key role in skeletal muscle regeneration. The infiltration of CD8 T cells into injured muscle has been reported. However, the role of CD8 T cells during skeletal muscle regeneration remains unclear. In this study, we used cardiotoxin-induced mouse skeletal muscle injury/regeneration model to investigate the role of CD8 T cells.
<>Muscle regeneration was impaired, and matrix deposit was increased in CD8α-deficient mice compared with wild-type (WT) mice whose CD8 T cells were infiltrated into damaged muscle after cardiotoxin injection. Adoptive transfer of CD8 T cells to CD8α-deficient mice improved muscle regeneration and inhibited matrix remodeling. Compared with WT mice, CD8α deficiency limited the recruitment of Gr1(high) macrophages (MPs) into muscle, resulting in the reduction of satellite cell number.
<>The expression of MCP-1 (MCP-1/CCL2), which regulates the migration of Gr1(high) MPs, was reduced in CD8α-deficient mice compared with WT mice. Coculture CD8 T cells with MPs promoted MCP-1 secretion. The i.m. injection of MCP-1 markedly promoted the recruitment of Gr1(high) MPs and improved muscle regeneration in CD8α-deficient mice. We conclude that CD8 T cells are involved in skeletal muscle regeneration by regulating the secretion of MCP-1 to recruit Gr1(high) MPs, which facilitate myoblast proliferation."[21]

Myokines

Myokines are chemicals secreted by muscles during exercise, or stimulation. They include Myostatin, TGF-b, VEGF, Interleukins, bDNF, & PGC1a, among others.

Exercise, most especially lactic acid-inducing exercise promotes bDNF production in slow twitch skeletal muscle [0], which is then is liable to diffuse into the bloodstream and pass the Blood Brain Barrier, promoting its neurotrophic effects, proving to me that the *slow twitch phenotype*, although less impressive in terms of hypertrophy potential (muscle size), is truly an essential component of healthy neurological aging, and offering another explanation for the intelligence differences present between low volume exercise powerlifters and strength trainers, versus high volume exercise Endurance Athletes:

"<>Exercise promotes brain plasticity partly by stimulating increases in mature brain-derived neurotrophic factor (mBDNF), but the role of the pro-BDNF isoform in the regulation of BDNF metabolism in humans is unknown. We quantified the expression of pro-BDNF and mBDNF in human skeletal muscle and plasma at rest, after acute exercise (+/- lactate infusion), and after fasting. Pro-BDNF and mBDNF were analyzed with immunoblotting, enzyme-linked immunosorbent assay, immunohistochemistry, and quantitative polymerase chain reaction.

<>Pro-BDNF was consistently and clearly detected in skeletal muscle (40-250 pg mg-1 dry muscle), whereas mBDNF was not. All methods showed a 4-fold greater pro-BDNF expression in type I muscle fibers compared to type II fibers. Exercise resulted in elevated plasma levels of mBDNF (55%) and pro-BDNF (20%), as well as muscle levels of pro-BDNF (∼10%, all $P < 0.05$). Lactate infusion during exercise induced a significantly greater increase in plasma mBDNF (115%, $P < 0.05$) compared to control (saline infusion), with no effect on pro-BDNF levels in plasma or muscle. A 3-day fast resulted in a small increase in plasma pro-BDNF (∼10%, $P < 0.05$), with no effect on mBDNF.
<>Pro-BDNF is highly expressed in human skeletal muscle, particularly in type I fibers, and is increased after exercise. While exercising with higher lactate augmented levels of plasma mBDNF, exercise-mediated increases in circulating mBDNF likely derive partly from release and cleavage of pro-BDNF from skeletal muscle, and partly from neural and other tissues.
<>These findings have implications for preclinical and clinical work related to a wide range of neurological disorders such as Alzheimer's, clinical depression, and amyotrophic lateral sclerosis."[21.0]
Of interest to myogenesis and adipose tissue: Peroxisome proliferator activated receptor-y (PPARy) [1] / Peroxisome Proliferator-Activated Receptor Alpha (PPARa) [2] and their upstream protein Peroxisome proliferator activated receptor-y gamma coactivator 1 alpha (PGC1a) [3], are influenced by many nutrients, phytochemicals, ergogenic chemicals, & training styles. Hypoxia positively associates with PGC1a activity (training in low oxygen conditions i.e. Endurance Training / High Volume Resistance Training). PGC1a is especially important for slow twitch muscle fiber growth, browning of fat, & brain cell function as it enhances mitochondrial biogenesis, angiogenesis, and even modulates satellite cell (stem cell) production. It may also promote the transformation of fast to slow twitch fibers, but I believe this process of muscle type transformation only occurs in severe cases of muscle damage. These proteins should be considered *Mitochondrial Factors*, for they play such a large role in mitochondrial dynamics:

[1] PPARy induces browning of white adipose tissue, while paradoxically promoting weight gain. In real world scenarios of enhanced PPARy activity, if a human diet is carefully controlled, and carbohydrates intake is mitigated, while chronic Aerobic or Endurance Training is pursued, it is unlikely that PPARy will exert pro-adipogenic effects.

"<>Peroxisome proliferator-activated receptor γ (PPARγ), a ligand-dependent transcription factor highly expressed in adipocytes, is a master regulator of adipogenesis and lipid storage, a central player in thermogenesis and an active modulator of lipid metabolism and insulin sensitivity. As a nuclear receptor governing numerous target genes, its specific signaling transduction relies on elegant transcriptional and post-translational regulations. Notably, in response to different metabolic stimuli, PPARγ recruits various cofactors and forms distinct transcriptional complexes that change

dynamically in components and epigenetic modification to ensure specific signal transduction.
<>Clinically, PPARγ activation via its full agonists, thiazolidinediones, has been shown to improve insulin sensitivity and induce browning of white fat, while undesirably induce weight gain, visceral obesity and other adverse effects."[22.0]

[2] PPARa promotes fatty acid oxidation, making it an essential mitochondrial component of both diet and exercise-induced lipolysis.

"<>In rodents, treatment with peroxisome proliferator-activated receptor alpha (PPARalpha) agonists results in peroxisome proliferation, hepatocellular hypertrophy, and hepatomegaly. Drugs in the fibrate class of PPARalpha agonists have also been reported to produce rare skeletal muscle toxicity. Although target-driven hepatic effects of PPARalpha treatment have been extensively studied, a characterization of the transcriptional effects of this nuclear receptor/transcription factor on skeletal muscle responses has not been reported.
<>In this study we investigated the effects of PPARalpha agonists on skeletal muscle gene transcription in rats. Further, since statins have been reported to preferentially effect type II muscle fibers, we compared PPARalpha signaling effects between type I and type II muscles. By comparing the transcriptional responses of agonists that signal through different nuclear receptors and using a selection/deselection analytical strategy based on ANOVA, we identified a PPARalpha activation signature that is evident in type I (soleus), but not type II (quadriceps femoris), skeletal muscle fibers. <>The fiber-type-selective nature of this response is consistent with increased fatty acid uptake and beta-oxidation, which represent the major clinical benefits of the hypolipidemic compounds used in this study, but does not reveal any obvious off-target pathways that may drive adverse effects."[22.1]

[3] PGC1a is preferentially expressed in slow twitch fibers, and it is capable of promoting muscle fiber transformation to oxidative types.

"<>The biochemical basis for the regulation of fibre-type determination in skeletal muscle is not well understood. In addition to the expression of particular myofibrillar proteins, type I (slow-twitch) fibres are much higher in mitochondrial content and are more dependent on oxidative metabolism than type II (fast-twitch) fibres. We have previously identified a transcriptional co-activator, peroxisome-proliferator-activated receptor-gamma co-activator-1 (PGC-1 alpha), which is expressed in several tissues including brown fat and skeletal muscle, and that activates mitochondrial biogenesis and oxidative metabolism.
<>We show here that PGC-1 alpha is expressed preferentially in muscle enriched in type I fibres. When PGC-1 alpha is expressed at physiological levels in transgenic mice driven by a muscle creatine kinase (MCK) promoter, a fibre type conversion is observed: muscles normally rich in type II fibres are redder and activate genes of mitochondrial oxidative metabolism. Notably, putative type II muscles from PGC-1 alpha transgenic

mice also express proteins characteristic of type I fibres, such as troponin I (slow) and myoglobin, and show a much greater resistance to electrically stimulated fatigue.
<>Using fibre-type-specific promoters, we show in cultured muscle cells that PGC-1 alpha activates transcription in cooperation with Mef2 proteins and serves as a target for calcineurin signalling, which has been implicated in slow fibre gene expression. These data indicate that PGC-1 alpha is a principal factor regulating muscle fibre type determination."[22.2]

[3.1] PGC1a promotes mitochondrial biogenesis, and maintains mitochondrial integrity.

"<>The majority of human energy metabolism occurs in skeletal muscle mitochondria emphasizing the importance of understanding the regulation of myocellular mitochondrial function. The transcriptional co-activator peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) has been characterized as a major factor in the transcriptional control of several mitochondrial components. Thus, PGC-1α is often described as a master regulator of mitochondrial biogenesis as well as a central player in regulating the antioxidant defense. However, accumulating evidence suggests that PGC-1α is also involved in the complex regulation of mitochondrial quality beyond biogenesis, which includes mitochondrial network dynamics and autophagic removal of damaged mitochondria.
<>In addition, mitochondrial reactive oxygen species production has been suggested to regulate skeletal muscle insulin sensitivity, which may also be influenced by PGC-1α. This review aims to highlight the current evidence for PGC-1α-mediated regulation of skeletal muscle mitochondrial function beyond the effects on mitochondrial biogenesis as well as the potential PGC-1α-related impact on insulin-stimulated glucose uptake in skeletal muscle.
<>Novelty: PGC-1α regulates mitochondrial biogenesis but also has effects on mitochondrial functions beyond biogenesis. Mitochondrial quality control mechanisms, including fission, fusion, and mitophagy, are regulated by PGC-1α. PGC-1α-mediated regulation of mitochondrial quality may affect age-related mitochondrial dysfunction and insulin sensitivity."[22.3]

[3.2] PGC1a ensures that Beta-oxidation is efficient, thus making exercise choice on a high fat diet a very important decision, such that if you only engage in low volume high load resistance training while on a traditional ketogenic diet, your body may begin to accumulate a far greater amount of toxic lipid waste products such as Ceramides.

"<>Peroxisome proliferator-activated receptor-gamma co-activator 1alpha (PGC1alpha) is a promiscuous co-activator that plays a key role in regulating mitochondrial biogenesis and fuel homeostasis. Emergent evidence links decreased skeletal muscle PGC1alpha activity and coincident impairments in mitochondrial performance to the development of insulin resistance in humans.

<>Here we used rodent models to demonstrate that muscle mitochondrial efficiency is compromised by diet-induced obesity and is subsequently rescued by exercise training. Chronic high fat feeding caused accelerated rates of incomplete fatty acid oxidation and accumulation of beta-oxidative intermediates. The capacity of muscle mitochondria to fully oxidize a heavy influx of fatty acid depended on factors such as fiber type and exercise training and was positively correlated with expression levels of PGC1alpha. Likewise, an efficient lipid-induced substrate switch in cultured myocytes depended on adenovirus-mediated increases in PGC1alpha expression.
<>Our results supported a novel paradigm in which a high lipid supply, occurring under conditions of low PGC1alpha, provokes a disconnect between mitochondrial beta-oxidation and tricarboxylic acid cycle activity.
<>Conversely, the metabolic remodeling that occurred in response to PGC1alpha overexpression favored a shift from incomplete to complete beta-oxidation. We proposed that PGC1alpha enables muscle mitochondria to better cope with a high lipid load, possibly reflecting a fundamental metabolic benefit of exercise training."[22.4]

[3.3] PGC1a is a "potent" regulator of exercise-induced angiogenesis, which is precisely why low volume training, regardless of the load lifted (light, moderate, heavy), is insufficient for promoting post-exercise increases in muscle angiogenesis.

"<>Aerobic metabolism requires oxygen and carbon sources brought to tissues via the vasculature. Metabolically active tissues such as skeletal muscle can regulate blood vessel density to match metabolic needs; however, the molecular cues that coordinate these processes remain poorly understood.
<>Here we report that the transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator-1β (PGC-1β), a potent regulator of mitochondrial biology, induces angiogenesis in skeletal muscle. PGC-1β induces the expression of vascular endothelial growth factor (VEGF) in cell culture and in vivo. The induction of VEGF by PGC-1β requires coactivation of the orphan nuclear receptor estrogen-related receptor-α (ERRα) and is independent of the hypoxia-inducible factor (HIF) pathway. In coculture experiments, overexpression of PGC-1β in skeletal myotubes increases the migration of adjacent endothelial cells, and this depends on VEGF signaling. Transgenic expression of PGC-1β in skeletal myocytes dramatically increases muscular vessel density.
<>Taken together, these data indicate that PGC-1β is a potent regulator of angiogenesis, thus providing a novel link between the regulations of oxidative metabolism and vascular density."[22.5]

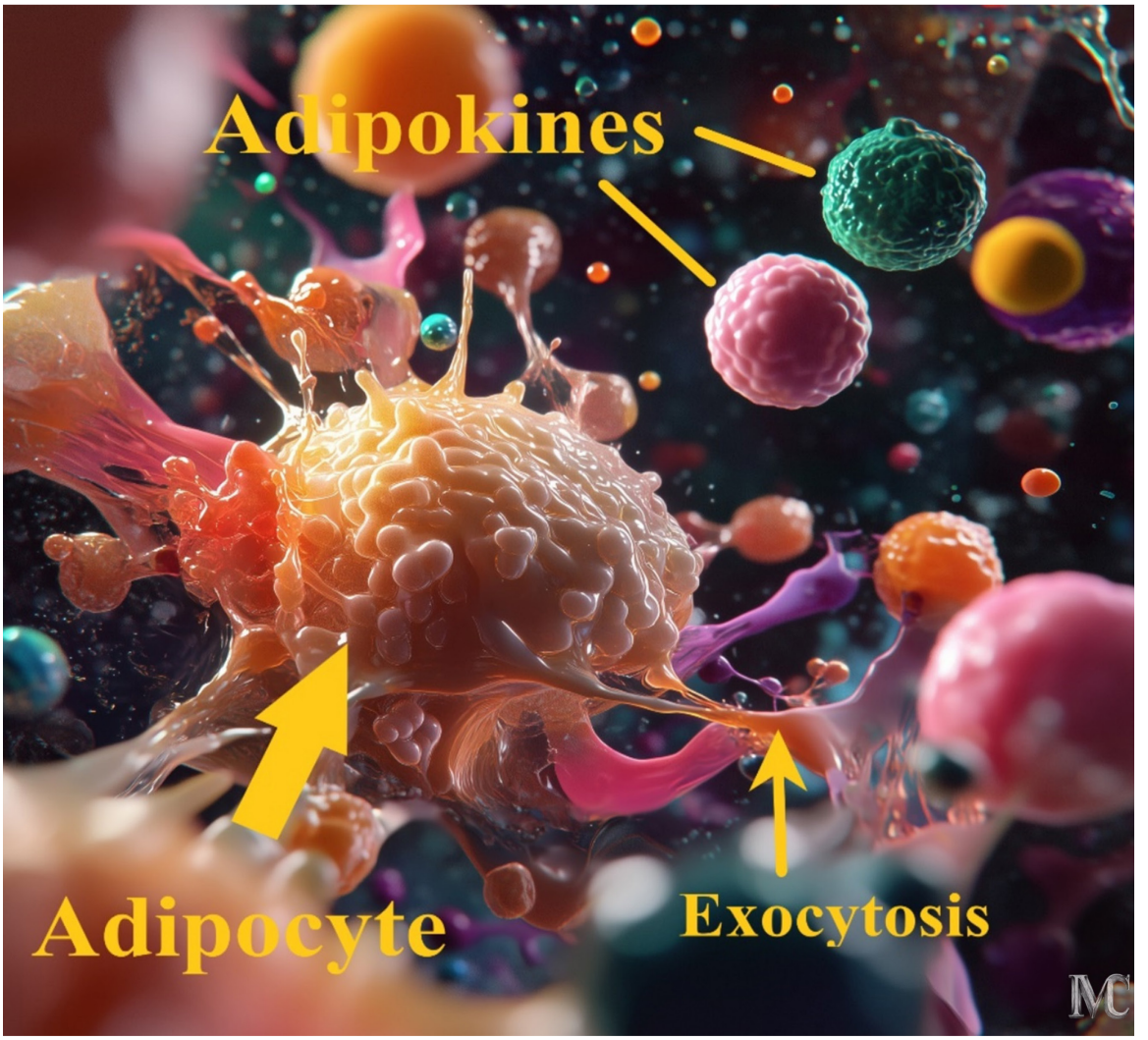
[3.4] PGC1a overexpression reduces absolute muscle stem cell number, but promotes increased stem cell proliferation, meaning it is more likely to influence Early Hypertrophy. Furthermore, this reduction in stem cell number versus proliferative potential is likely a direct connection to the anti-aging benefit of Endurance Training on muscles, considering the stem cell pool is not as liable to become continuously over-exhausted from each exercise session, leading to lessened aging and exercise-induced progressive muscle stem cell senescence.

"<>Background: The myogenic capacity of satellite cells (SCs), adult muscle stem cells, is influenced by aging, exercise, and other factors. In skeletal muscle, the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) is a key regulator of oxidative metabolism and endurance training adaptation. However, a link between PGC-1α and SC behavior remains unexplored.
<>Methods: We have now studied SC function in a PGC-1α fiber-specific gain-of-function animal model.
<>Results: In surprising contrast to bona fide exercise, muscle-specific PGC-1α transgenic mice have lower SC numbers. Nevertheless, SCs from these mice have a higher propensity for activation and proliferation. Intriguingly, muscle PGC-1α triggers a remodeling of the SC niche by altering the extracellular matrix composition, including the levels of fibronectin, which affects the proliferative output of SCs.
<>Conclusions: Taken together, PGC-1α indirectly affects SC plasticity in skeletal muscle and thereby might contribute to improved SC activation in exercise."
↓ continued
"<>Very surprisingly, the fiber-type shift mediated by muscle PGC-1α was not linked to an increase in SC numbers, as would be expected from more oxidative or endurance-trained muscle beds. In fact, transgenic overexpression of PGC-1α consistently resulted in lower SC counts, both in muscle in vivo and in fiber/SC preparations ex vivo. This divergence is one of the very few parameters for which the PGC-1α-overexpressing and bona fide oxidative fibers are clearly different. In regard to most other metabolic and contractile properties, skeletal muscles of mTG animals closely mimic the phenotype of oxidative muscles.
<>Thus, the mechanistic underpinnings that control the diametrically opposite outcome between PGC-1α-overexpressing fibers with low vis-à-vis oxidative and endurance-trained muscle with high SC count is unclear. Importantly, this reduction in SC numbers was however offset by the higher proliferative potential of SCs in the mTG animals. At least this aspect could represent the contribution of muscle PGC-1α to SC biology in exercise."[22.6]

Adipokines

Adipokines are chemicals secreted by adipose tissue (fat), they are produced within the adipocyte cell and stored in adipocyte vesicles, where they are released through a process called Exocytosis. Adipokines include many pro-inflammatory factors such as IL-6, IL-1B, TNF-a, and even Mesenchymal Stem Cells, & Aromatase. Although these factors do not come solely from adipose tissue, it is merely one producer.
Adipose tissue clearly promotes myogenesis if moderately active, yet when adiposity reaches a certain unknown threshold (possibly over 30% body fat), it becomes deleterious to muscle growth due to promoting excessive inflammation.

Because adipokines are primarily inflammatory, it is my conclusion that they are relatively useless towards Anti-Inflammation lifestyles, where phytochemicals suppress or outright inhibit IL-6 and TNF-a, to exert their antioxidant effects, although one may argue against this point by pointing out the fact that even without active inflammation, the secreted Mesenchymal Stem Cells will exert an anabolic effect, I would politely disagree, considering the majority of Stem Cells that facilitate Myogenesis originate from blood vessels.



Obesity becomes primarily an *estrogenic eyesore* when inflammation is inhibited, which is why it does not make logical sense to maintain a hypercaloric (high energy) diet if you are obese whilst taking numerous phytochemical / mycochemicals antioxidants and essential nutrients, such as many overweight individuals tend to do, falsely assuming that the metabolic machinery of their biology is strengthened through a reduction in inflammation and ROS.

We should now understand that when people “bulk”, or overfeed for extends periods of time, and gain weight, that the increased muscle strength and hypertrophy that accompanies this is not only because of the increased supply of energy, but because of the increased release of anabolic Adipokines.

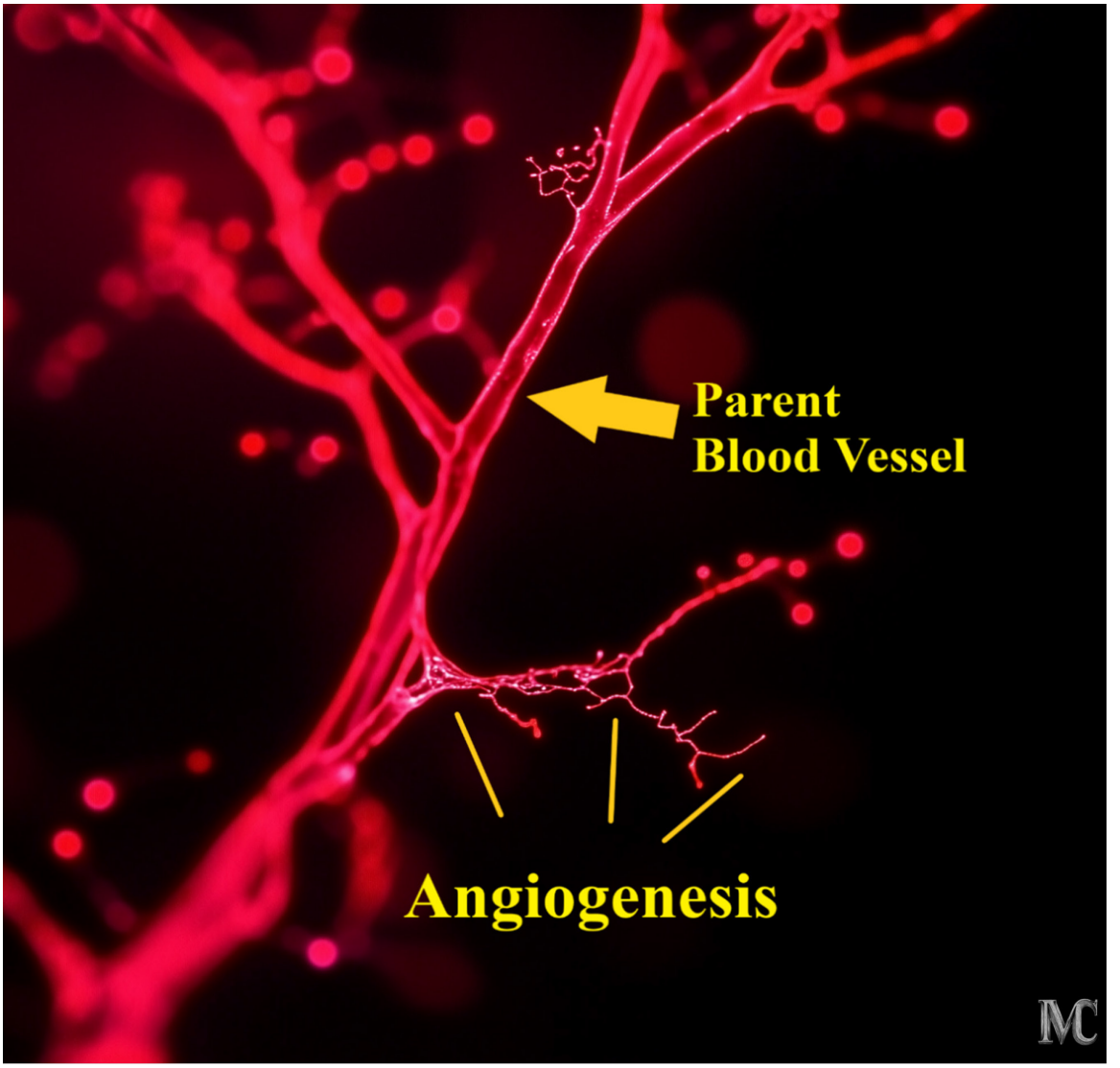
Angiogenesis

The neglected and rarely spoken of mechanism in muscle / brain regeneration, and cardiac health, and what I consider to be the most important science of the 21st Century towards enriching human health.
Angiogenesis, the sprouting of new blood vessels from pre-existing blood vessels, is often vilified as a positive process in tumor development, but a lack thereof in muscle and brain tissue leads to accelerated aging & delayed wound regeneration. It is true that increasing blood vessel growth in your muscles through modalities and supplementation will benefit you tremendously, but without cardiac and neurological angiogenesis, attained primarily from high-lactate generating exercise such as high intensity interval cardio, or steady-state cardio, you will do yourself a great disfavor by missing the opportunity at promoting life extension and cognition.

Skeletal muscle angiogenesis occurs primarily through shear stress which is a mechanical force that occurs when blood flow patterns and velocities change in muscle tissue during exercise. When the skeletal muscle blood flow rate is increased, the force of this change stimulates the endothelial lining of blood vessels to activate the Akt & ERK pathways to initiate adaptation through angiogenesis. Skeletal muscle angiogenesis is not uniform; it is specific to muscle fiber type dependent on exercise style and duration. Higher volume exercise will always promote angiogenesis to a greater extent than lower volume exercise, and this is simply because there are greater increases in muscle blood flow during high volume exercise, and this is true ever for explosive movements, such that training with resistance bands and performing dozens of repetitions with an explosive tempo will cause greater increases to fast twitch fiber angiogenesis than antiquated high load “speedwork”.
Because muscle blood flow is essential to regeneration to growth (myogenesis), Vascular Deconditioning (Capillary Regression), is a homeostatic and pathogenic process that occurs in muscle tissue and cardiovascular tissue during inactivity, and it will always parallel muscle strength and endurance losses, whereas absolute strength, or muscle power, is dependent on the CNS and neuromuscular synapses of muscle tissue.

Shear stress is a mechanical force that occurs when adjacent layers of fluid, such as blood, flow at different velocities or in different directions. In the context of blood vessels, shear stress is the frictional force exerted by blood flow on the endothelial cells lining the vessel walls. Regular physical exercise can increase shear stress within blood vessels, particularly those supplying skeletal muscles.

Blood vessels are essential for oxygen and nutrient delivery, but more impressively blood vessels release their own form of myogenic stem cells called pericytes. Facilitating angiogenesis is truly the future of performance enhancement, both neurologically and muscularly. Endurance exercise tends to enhance angiogenesis in slow twitch fibers, just as high intensity and strength training exercise tends to enhance angiogenesis in fast twitch fibers. The process of adult skeletal muscle or neurological angiogenesis generally occurs when a protein called Vascular Endothelial Growth Factor A (VEGF-A) increases, usually by the Free Radical called Nitric Oxide, or through exogenous chemical use, causing endothelial cells to proliferate, and angiogenesis to occur. There is also another angiogenic protein called Basic Fibroblast Growth Factor, that of which is rarely produced in adult skeletal muscle tissue, aside from the consumption of a certain primordial byproduct of fermentation.



There are two similar but different angiogenic processes that occur in skeletal muscle and brain tissue. The first angiogenic process may be called Traditional Angiogenesis, or as I refer to it, *Capillary Hyperplasia*, it involves the growth of new blood vessels from preexisting blood vessels, this process is dependent on increased Endothelial Cell Proliferation. The second and distinct angiogenic process is what I refer to as *Capillary Hypertrophy*, it requires increased Endothelial Cell Migration, it results in preexisting capillary maintenance and growth. Capillary Hyperplasia is involved in all stages of Myogenesis, as new muscle tissue must be innervated with blood vessels to both regenerate and grow effectively, and the more capillaries present in a muscle the more pericytes are released. Capillary Hypertrophy is more related to muscle strength-endurance, as larger capillaries allow a greater amount of oxygen and nutrients to reach targeted areas of muscles.

Angiogenesis is an accumulative process, in that it takes chronic elevations in VEGF-A or other angiogenic growth factors, during the process of wound healing, to facilitate angiogenesis. This is why the more often a muscle is trained in a week, the greater the capillary density of said muscle is to be found, thus explaining why aerobic exercise is so angiogenic, for it is not only high volume, but performed at a high frequency.

[A] Pericytes regenerate damaged muscle tissue.

"<>Multipotent stem/progenitor cells with similar developmental potentials have been independently identified from diverse human tissue/organ cultures. The increasing recognition of the vascular/perivascular origin of mesenchymal precursors suggested blood vessels being a systemic source of adult stem/progenitor cells. Our group and other laboratories recently isolated multiple stem/progenitor cell subsets from blood vessels of adult human tissues.

<>Each of the three structural layers of blood vessels: intima, media, and adventitia has been found to include at least one precursor population, that is, myogenic endothelial cells (MECs), pericytes, and adventitial cells (ACs), respectively. MECs and pericytes efficiently regenerate myofibers in injured and dystrophic skeletal muscles as well as improve cardiac function after myocardial infarction. The applications of ACs in vascular remodeling and angiogenesis/vasculogenesis have been examined.

<>Our recent finding that MECs and pericytes can be purified from cryogenically banked human primary muscle cell culture further indicates their potential applications in personalized regenerative medicine."[23]

[B] Angiogenesis plays a vital role in cognition.

"<>Aerobic exercise has been well established to promote enhanced learning and memory in both human and non-human animals. Exercise regimens enhance blood perfusion, neo-vascularization, and neurogenesis in nervous system structures associated with learning and memory. The impact of specific plastic changes to learning and memory performance in exercising animals are not well understood. The current

experiment was designed to investigate the contributions of angiogenesis and neurogenesis to learning and memory performance by pharmacologically blocking each process in separate groups of exercising animals prior to visual spatial memory assessment.
<>Results from our experiment indicate that angiogenesis is an important component of learning as animals receiving an angiogenesis inhibitor exhibit retarded Morris water maze (MWM) acquisition. Interestingly, our results also revealed that neurogenesis inhibition improves learning and memory performance in the MWM. Animals that received the neurogenesis inhibitor displayed the best overall MWM performance. These results point to the importance of vascular plasticity in learning and memory function and provide empirical evidence to support the use of manipulations that enhance vascular plasticity to improve cognitive function and protect against natural cognitive decline.[24]

[C] Lactate produced by muscles during intense exercise promotes angiogenesis in the brain.

"Physical exercise can improve brain function and delay neurodegeneration; however, the initial signal from muscle to brain is unknown. Here we show that the lactate receptor (HCAR1) is highly enriched in pial fibroblast-like cells that line the vessels supplying blood to the brain, and in pericyte-like cells along intracerebral microvessels. Activation of HCAR1 enhances cerebral vascular endothelial growth factor A (VEGFA) and cerebral angiogenesis. High-intensity interval exercise (5 days weekly for 7 weeks), as well as L-lactate subcutaneous injection that leads to an increase in blood lactate levels similar to exercise, increases brain VEGFA protein and capillary density in wild-type mice, but not in knockout mice lacking HCAR1. In contrast, skeletal muscle shows no vascular HCAR1 expression and no HCAR1-dependent change in vascularization induced by exercise or lactate. Thus, we demonstrate that a substance released by exercising skeletal muscle induces supportive effects in brain through an identified receptor."[25]

[D] Capillary growth is predominantly related to myofiber growth.

“<>Twelve male subjects with recreational resistance training backgrounds completed 12 wk of intensified resistance training (3 sessions/wk; 8 exercises/session; 3 sets/exercise; 10 repetitions maximum/set). All major muscle groups were trained, with four exercises emphasizing the forearm flexors. After training, strength (1-repetition maximum preacher curl) increased by 25% ($P < 0.05$). Magnetic resonance imaging scans revealed an increase in the biceps brachii muscle cross-sectional area (CSA) (from 11.8 +/- 2.7 to 13.3 +/- 2.6 cm2; $n = 8$; $P < 0.05$). Muscle biopsies of the biceps brachii revealed increases ($P < 0.05$) in fiber areas for type I (from 4,196 +/- 859 to 4,617 +/- 1,116 microns2; $n = 11$) and II fibers (from 6,378 +/- 1,552 to 7,474 +/- 2,017 microns2; $n = 11$). Fiber number estimated from the above measurements did not change after training (293.2 +/- 61.5 x 10(3) pretraining; 297.5 +/- 69.5 x 10(3) posttraining; $n = 8$).

<>However, the magnitude of muscle fiber hypertrophy may influence this response because those subjects with less relative muscle fiber hypertrophy, but similar increases in muscle CSA, showed evidence of an increase in fiber number. Capillaries per fiber increased significantly ($P < 0.05$) for both type I (from 4.9 +/- 0.6 to 5.5 +/- 0.7; $n = 10$) and II fibers (from 5.1 +/- 0.8 to 6.2 +/- 0.7; $n = 10$). No changes occurred in capillaries per fiber area or muscle area. In conclusion, resistance training resulted in hypertrophy of the total muscle CSA and fiber areas with no change in estimated fiber number, whereas capillary changes were proportional to muscle fiber growth."[26]

[E] VEGF is essential for exercise-induced neurogenesis. This is great example of why high volume training is essential to any exercise protocol designed to enhance cognition.

"<>Key points: Peripheral vascular endothelial growth factor (VEGF) is necessary for exercise to stimulate hippocampal neurogenesis. Here we report that skeletal myofiber VEGF directly or indirectly regulates exercise-signalled proliferation of neuronal precursor cells. Our results found skeletal myofiber VEGF to be necessary for maintaining blood flow through hippocampal regions independent of exercise training state. This study demonstrates that skeletal myofiber VEGF is required for the hippocampal VEGF response to acute exercise. These results help to establish the mechanisms by which exercise, through skeletal myofiber VEGF, affects the hippocampus.
<>Abstract: Exercise signals neurogenesis in the dentate gyrus of the hippocampus. This phenomenon requires vascular endothelial growth factor (VEGF) originating from outside the blood-brain barrier, but no cellular source has been identified. Thus, we hypothesized that VEGF produced by skeletal myofibers plays a role in regulating hippocampal neuronal precursor cell proliferation following exercise training. This was tested in adult conditional skeletal myofiber-specific VEGF gene-ablated mice (VEGFHSA-/-) by providing VEGFHSA-/- and non-ablated (VEGFf/f) littermates with running wheels for 14 days. Following this training period, hippocampal cerebral blood flow (CBF) was measured by functional magnetic resonance imaging (fMRI), and neuronal precursor cells (BrdU+/Nestin+) were detected by immunofluorescence. The VEGFf/f trained group showed improvements in both speed and endurance capacity in acute treadmill running tests ($P < 0.05$). The VEGFHSA-/- group did not.
<>The number of proliferating neuronal precursor cells was increased with training in VEGFf/f ($P < 0.05$) but not in VEGFHSA-/- mice. Endothelial cell (CD31+) number did not change in this region with exercise training or skeletal myofiber VEGF gene deletion. However, resting blood flow through the hippocampal region was lower in VEGFHSA-/- mice, both untrained and trained, than untrained VEGFf/f mice ($P < 0.05$). An acute hypoxic challenge decreased CBF ($P < 0.05$) in untrained VEGFf/f , untrained VEGFHSA-/- and trained VEGFHSA-/- mice, but not trained VEGFf/f mice. VEGFf/f , but not VEGFHSA-/- , mice were able to acutely run on a treadmill at an intensity sufficient to increase hippocampus VEGF levels. These data suggest that VEGF expressed by skeletal myofibers may directly or indirectly regulate both hippocampal blood flow and neurogenesis."[26.1]

[F] Quiescent (Dormant) Endothelial Cells promote Beta-Oxidation (Fatty acid breakdown: Lipolysis) which result in *NADPH formation, this means that because angiogenesis accompanies endothelial cell proliferation, the more blood vessels you form in your body, the greater Beta-Oxidation you will possess in later life, which may be beneficial or detrimental to your overall health, depending on your diet.

If you are a fast twitch athlete that consumes large amounts of carbohydrates, the formation of new blood vessels beyond a certain point, and after a certain *age of quiescence*, will cause metabolic issues. For more information on these sciences refer to the sections Fasting (Substrate Competition) / Adipocytes, Adipogenesis, & Lipolysis.

The following study also describes the benefits of Acetate (Vinegar) in promoting Endothelial quiescence.

*NADPH is similar to NAD+ in that they both promote longevity, but NADPH only serves the role of an endogenously produced antioxidant, whereas NAD+ participates in DNA repair & stress resistance through activating Sirtuins.

"<>Little is known about the metabolism of quiescent endothelial cells (QECs). Nonetheless, when dysfunctional, QECs contribute to multiple diseases. Previously, we demonstrated that proliferating endothelial cells (PECs) use fatty acid β-oxidation (FAO) for de novo dNTP synthesis. We report now that QECs are not hypometabolic, but upregulate FAO >3-fold higher than PECs, not to support biomass or energy production but to sustain the tricarboxylic acid cycle for redox homeostasis through NADPH regeneration.
<>Hence, endothelial loss of FAO-controlling CPT1A in CPT1AΔEC mice promotes EC dysfunction (leukocyte infiltration, barrier disruption) by increasing endothelial oxidative stress, rendering CPT1AΔEC mice more susceptible to LPS and inflammatory bowel disease. Mechanistically, Notch1 orchestrates the use of FAO for redox balance in QECs.
<>Supplementation of acetate (metabolized to acetyl-coenzyme A) restores endothelial quiescence and counters oxidative stress-mediated EC dysfunction in CPT1AΔEC mice, offering therapeutic opportunities. Thus, QECs use FAO for vasculoprotection against oxidative stress-prone exposure."[26.2]

[G] Activating Transcription Factor 3/4 muscle endothelial cells (mEC) are activated during cellular stress, such as hypoxia, and upregulate VEGF expression. Slow twitch muscle fibers are inherently more angiogenic than their glycolytic counterparts due to being "metabolically primed" for angiogenesis, thus providing more evidence for the benefits of endurance training, or any form of high volume exercise. Interestingly, the enrichment of a non-essential amino acid mixture containing L-Alanine, L-Asparagine, L-Aspartic Acid, L-Glutamic Acid, Glycine, L-Proline, & L-Serine promotes angiogenesis in glycolytic fibers, which leads me to the conclusion that amino acid restriction leads to enhanced slow twitch fiber-specific angiogenesis, whereas macronutrient excess, especially non-essential amino acids, leads to enhanced fast twitch fiber angiogenesis.

"<>Exercise is a powerful driver of physiological angiogenesis during adulthood, but the mechanisms of exercise-induced vascular expansion are poorly understood. We explored endothelial heterogeneity in skeletal muscle and identified two capillary muscle endothelial cell (mEC) populations that are characterized by differential expression of ATF3/4. Spatial mapping showed that ATF3/4+ mECs are enriched in red oxidative muscle areas while ATF3/4low ECs lie adjacent to white glycolytic fibers.
<>In vitro and in vivo experiments revealed that red ATF3/4+ mECs are more angiogenic when compared with white ATF3/4low mECs. Mechanistically, ATF3/4 in mECs control genes involved in amino acid uptake and metabolism and metabolically prime red (ATF3/4+) mECs for angiogenesis. As a consequence, supplementation of non-essential amino acids and overexpression of ATF4 increased proliferation of white mECs.
<>Finally, deleting Atf4 in ECs impaired exercise-induced angiogenesis. Our findings illustrate that spatial metabolic angiodiversity determines the angiogenic potential of muscle ECs."[26.3]

[See: Detraining, Deloading, & Vascular Deconditioning]

Myogenic Regulatory Factors (MRF's)

The common Myogenic Regulatory Factors are Myf5, MyoD, Myogenin, & MRF4.

MyoD & Myf5 appear to be the most important MRF's as they associate with both the early & late stages of myogenesis, followed by MRF4 & Myogenin which participate in the late stages of myogenesis.

"<>The MRF expression program during satellite cell activation, proliferation, and differentiation is analogous to the program manifested during the embryonic development of skeletal muscle. During in vitro single muscle fiber culture and in vivo muscle regeneration, in which satellite cells initiate their activation and entrance into the cell cycle, either MyoD or Myf5 is rapidly upregulated concomitant with entrance of the cell cycle, followed soon after by coexpression of MyoD and Myf5. Following proliferation. Myogenin and MRF4 are expressed in cells beginning their differentiation program. Therefore. MyoD and Myf5 appear to play an early role in the satellite cell developmental program."[27]

Myoblast Determination Protein 1 (MyoD)
+ Myogenic Regulatory Factor 5 (MRF5)

MyoD & MYF-5 are similarly functioning essential MRF's for hypertrophy and hyperplasia, and especially stem cell recruitment into damaged muscle tissue.

[A] "<>Mice lacking MyoD gene display marked deficits in satellite cell function. MyoD mutant mice interbred with mdx mice. In spite of the presence of morphologically normal

satellite cells in MyoD–/– muscles. muscle from MyoD–/– mice displays a strikingly reduced capacity for regeneration following injury. By contrast, Myf5 expression is markedly upregulated in these cells. Under conditions that normally induce differentiation of wild-type myoblasts, MyoD–/– myoblasts continue to proliferate and exhibit delayed differentiation. Supporting this, MyoD–/–: myoblasts show delayed induction of myogenin and MRF4.
<>Therefore. MyoD–/– myoblasts display characters that are more primitive than wild-type myoblasts and may represent an intermediate stage between a satellite cell and a myogenic precursor cell."[28]

[A2] "<>Null mutations for the MyoD gene generate no skeletal muscle phenotype due to a compensatory activation of the Myf-5 gene."
"<>While skeletal myogenesis in these mutant mice resumes normally at the onset of MyoD expression, a skeletal defect of the ribs persists. "
"<>Apparently, Myf-5 and MyoD individually are not absolutely essential for skeletal muscle development, most likely because they have overlapping or redundant functions. In fact, double mutants lacking both, MyoD and Myf-5, fail to develop skeletal musculature and the muscle forming regions seem to be devoid of myoblasts."[29]

[A3] MyoD promotes VEGF expression in skeletal muscle.

"<>These predictions led us to test whether MyoD regulates VEGF expression during the muscle differentiation program. In C2C12 cells we stably overexpressed a control vector, a wild-type MyoD, or a dominant negative MyoD (dnMyoD) in which MyoD is fused to the lysosomal protease cathepsin B, thus proteolytically digesting any MyoD multimers and/or detour the multimers from their usual subcellular destination to the lysosome (Li et al., 1996 blue right-pointing triangle). We then used semiquantitative RT-PCR to examine the endogenous VEGF expression levels in each condition.
<>Overexpression of wild-type MyoD led to a significant increase in VEGF isoform levels over the control condition, whereas dnMyoD expression resulted in a marked reduction in VEGF isoform expression compared with the control. These data suggest that MyoD is necessary to maintain a baseline level of VEGF transcriptional expression in C2C12."[30]

Myogenin (MYOG) + Myogenic Factor 6 (MRF4)

[A] "<>Homozygous inactivation of the myogenin gene leads to drastically reduced myofiber formation. These mice accumulate apparently normal numbers of myoblasts which are arrested in their terminal differentiation program."[31]

[A2]" <>Myogenin expression happens later and is crucial for terminal differentiation, while Mrf4 promotes both fate determination and differentiation."[32]
(Terminal Differentiation is the final stage of Differentiation).

[B] “<>Myf-6 null mutant mice exhibit drastically reduced expression of Myf-5 for reasons presently unknown. The phenotype is very similar to Myf-5 mutants with an additional reduction of deep back muscles and minor alterations in sarcomeric protein isoforms.”[33]

[C] MRF4 (MRF6) suppresses myogenesis through suppressing MEF2.

"<>The myogenic regulatory factor MRF4 is highly expressed in adult skeletal muscle but its function is unknown. Here we show that Mrf4 knockdown in adult muscle induces hypertrophy and prevents denervation-induced atrophy. This effect is accompanied by increased protein synthesis and widespread activation of muscle-specific genes, many of which are targets of MEF2 transcription factors. MEF2-dependent genes represent the top-ranking gene set enriched after Mrf4 RNAi and a MEF2 reporter is inhibited by co-transfected MRF4 and activated by Mrf4 RNAi. The Mrf4 RNAi-dependent increase in fibre size is prevented by dominant negative MEF2, while constitutively active MEF2 is able to induce myofibre hypertrophy.

<>The nuclear localization of the MEF2 corepressor HDAC4 is impaired by Mrf4 knockdown, suggesting that MRF4 acts by stabilizing a repressor complex that controls MEF2 activity. These findings open new perspectives in the search for therapeutic targets to prevent muscle wasting, in particular sarcopenia and cachexia."[34]

[C2] MRF4 (MRF6) although being suppressive of myogenesis is essential for neuromuscular junction function, complicating the situation.
[See: Anti-Inflammation Supplementation: Creatine Monohydrate]

“<>MRF4 belongs to the basic helix-loop-helix class of transcription factors and this and other members of its family profoundly influence skeletal muscle development. Less is known about the role of these factors in aging. As MRF4 is preferentially expressed in subsynaptic nuclei, we postulated it might play a role in maintenance of the neuromuscular junction.
<>To test this hypothesis, we examined the junctional regions of 19-20-month-old mice and found decreased levels of SV2B, a marker of synaptic vesicles, in MRF4-null mice relative to controls. There was a corresponding decrease in grip strength in MRF4-null mice.
<>Taken together, these data suggest that the intrinsic muscle factor, MRF4 plays an important role in maintenance of neuromuscular junctions.”[35]

Paired Box Protein (PAX7)

PAX7 promotes myogenic proliferation and has a negligible effect on differentiation.

“<>Skeletal muscle growth and regeneration are attributed to satellite cells - muscle stem cells resident beneath the basal lamina that surrounds each myofibre. Quiescent satellite

cells express the transcription factor Pax7 and when activated, coexpress Pax7 with MyoD. Most then proliferate, downregulate Pax7 and differentiate. By contrast, others maintain Pax7 but lose MyoD and return to a state resembling quiescence.
<>Here we show that Pax7 is able to drive transcription in quiescent and activated satellite cells, and continues to do so in those cells that subsequently cease proliferation and withdraw from immediate differentiation. We found that constitutive expression of Pax7 in satellite-cell-derived myoblasts did not affect MyoD expression or proliferation. Although maintained expression of Pax7 delayed the onset of myogenin expression it did not prevent, and was compatible with, myogenic differentiation. Constitutive Pax7 expression in a Pax7-null C2C12 subclone increased the proportion of cells expressing MyoD, showing that Pax7 can act genetically upstream of MyoD. However, these Pax7-null cells were unable to differentiate into normal myotubes in the presence of Pax7.
<>Therefore, Pax7 may be involved in maintaining proliferation and preventing precocious differentiation, but does not promote quiescence."[36]

Other Myogenic Proteins

Phosphoinositide 3-Kinase (PI3K) and Protein Kinase B (AKT) are a group of proteins that activate in response to diet or exogenous chemical use and result in a cascade of effects, such as increased mTOR activity. mTORC1 plays a vital part in initiating early myogenesis & neurogenesis through promoting stem cell production. The notable upstream signals of mTORC1 are ERK1/2, WNT Signaling, & certain Cytokines. mTOR also promotes adipogenesis and certain forms of neurological memory. mTORC2 is associated more with the end stages of myogenesis (terminal differentiation).

"<>Growth factor induced activation of phosphoinositide 3-kinase and protein kinase B (PKB) leads to increased activity of the mammalian target of rapamycin (mTOR). This subsequently leads to increased phosphorylation of eIF4E binding protein-1 (4EBP1) and activation of p70 ribosomal S6 protein kinase (p70(S6K)), both of which are important steps in the stimulation of protein translation. The stimulation of translation is attenuated in cells deprived of amino acids and this is associated with the attenuation of 4EBP1 phosphorylation and p70(S6K) activation. It has been suggested that PKB regulates mTOR function by phosphorylation although direct phosphorylation of mTOR by PKB has not been demonstrated previously.
<>In the present work, we have found that PKB directly phosphorylates mTOR and, using phosphospecific antibodies, we have shown this phosphorylation occurs at Ser(2448). Insulin also induces phosphorylation on Ser(2448) and this effect is blocked by wortmannin but not rapamycin, consistent with the effect being mediated by PKB. Amino-acid starvation rapidly attenuated the reactivity of the Ser(2448) phosphospecific antibody with mTOR and this could not be restored by either insulin stimulation of cells or incubation with PKB in vitro. Our findings demonstrate that mTOR is a direct target for PKB and support the conclusion that regulation of phosphorylation of Ser(2448) is a

point of convergence for the counteracting regulatory effects of growth factors and amino acid levels."[37.0]

"<>mTOR phosphorylates 4E-BP1 and p70S6K. mTOR can be activated by a variety of stimuli, including amino acids, contractile activity, insulin, IGF-I, and other growth factors."[37]

Mechanistic Target of Rapamycin 1-2 (mTORC1/2), P70S6K, & 4E-BP1/2

[A] mTORC1 is essential for mechanical load-induced hypertrophy but not protein synthesis, meaning that it is not essential for maintaining muscle, only growing muscle.

"<>It is well known that an increase in mechanical loading can induce skeletal muscle hypertrophy, and a long-standing model in the field indicates that mechanical loads induce hypertrophy via a mechanism that requires signaling through the mechanistic target of rapamycin complex 1 (mTORC1). Specifically, it has been widely proposed that mechanical loads activate signaling through mTORC1 and that this, in turn, promotes an increase in the rate of protein synthesis and the subsequent hypertrophic response. However, this model is based on a number of important assumptions that have not been rigorously tested.
<>In this study, we created skeletal muscle specific and inducible raptor knockout mice to eliminate signaling by mTORC1, and with these mice we were able to directly demonstrate that mechanical stimuli can activate signaling by mTORC1, and that mTORC1 is necessary for mechanical load-induced hypertrophy. Surprisingly, however, we also obtained multiple lines of evidence that indicate that mTORC1 is not required for a mechanical load-induced increase in the rate of protein synthesis. <>This observation highlights an important shortcoming in our understanding of how mechanical loads induce hypertrophy and illustrates that additional mTORC1-independent mechanisms play a critical role in this process."[38]

[A2] mTORC1 ablation reduces both myogenic proliferation (early hypertrophy), and myogenic differentiation (secondary hypertrophy).

"<>The serine/threonine kinase mammalian target of rapamycin (mTOR) is a key regulator of protein synthesis, cell proliferation and energy metabolism. As constitutive deletion of Mtor gene results in embryonic lethality, the function of mTOR in muscle stem cells (satellite cells) and skeletal muscle regeneration remains to be determined.
<>In this study, we established a satellite cell specific Mtor conditional knockout (cKO) mouse model by crossing Pax7CreER and Mtorflox/flox mice. Skeletal muscle regeneration after injury was severely compromised in the absence of Mtor, indicated by increased number of necrotic myofibers infiltrated by Evans blue dye, and reduced number and size of regenerated myofibers in the Mtor cKO mice compared to wild type (WT) littermates.

<>To dissect the cellular mechanism, we analyzed satellite cell-derived primary myoblasts grown on single myofibers or adhered to culture plates. The Mtor cKO myoblasts exhibited defective proliferation and differentiation kinetics when compared to myoblasts derived from WT littermates. At the mRNA and protein levels, the Mtor cKO myoblasts expressed lower levels of key myogenic determinant genes Pax7, Myf5, Myod, Myog than did the WT myoblasts.
<>These results suggest that mTOR is essential for satellite cell function and skeletal muscle regeneration through controlling the expression of myogenic genes."[38.1]

[B] mTORC2 is essential for myogenic differentiation.

"<>Rapamycin, a selective inhibitor of mTORC1 signaling, blocks terminal myoblast differentiation. We found that downregulation of rictor, a component of the mTORC2 complex, but not downregulation of raptor, a component of the mTORC1 complex, prevented terminal differentiation (fusion) of C2C12 myoblasts. Both rapamycin and rictor downregulation suppressed the phosphorylation of AKT(S(473)), and rapamycin treatment of C2C12 myoblasts disrupted the mTORC2 complex. Importantly, downregulation of rictor inhibited TORC2 signaling without inhibiting mTORC1 signaling, suggesting that inhibition of mTORC1 by rapamycin may not be the cause of arrested differentiation. In support of this, expression of a phosphomimetic mutant AKT(S473D) in rictor-deficient cells rescued myoblast fusion even in the presence of rapamycin.
<>mTORC2 signaling to AKT appears necessary for downregulation of the Rho-associated kinase (ROCK1) that occurs during myogenic differentiation. Rapamycin treatment prevented ROCK1 inactivation during differentiation, while suppression of ROCK1 activity during differentiation and myoblast fusion was restored through expression of AKT(S473D), even in the presence of rapamycin. Further, the ROCK inhibitor Y-27632 restored terminal differentiation in rapamycin-treated myoblasts. These results provide the first evidence of a specific role for mTORC2 signaling in terminal myogenic differentiation."[39]

[C] P70SK6 is a marker hypertrophy and increases primarily through high load exercise.

"<>High-resistance exercise training results in an increase in muscle wet mass and protein content. To begin to address the acute changes following a single bout of high-resistance exercise, a new model has been developed. Training rats twice a week for 6 wk resulted in 13.9 and 14.4% hypertrophy in the extensor digitorum longus (EDL) and tibialis anterior (TA) muscles, respectively. Polysome profiles after high-resistance lengthening contractions suggest that the rate of initiation is increased. The activity of the 70-kDa S6 protein kinase (p70(S6k)), a regulator of translation initiation, is also increased following high-resistance lengthening contractions (TA, 363 +/- 29%; EDL, 353 +/- 39%).
<>Furthermore, the increase in p70(S6k) activity 6 h after exercise correlates with the percent change in muscle mass after 6 wk of training (r = 0.998). The tight correlation

between the activation of p70(S6k) and the long-term increase in muscle mass suggests that p70(S6k) phosphorylation may be a good marker for the phenotypic changes that characterize muscle hypertrophy and may play a role in load-induced skeletal muscle growth."[40]

[E] mTORC1 is crucial for memory consolidation.

"<>Mechanistic Target Of Rapamycin Complex 1 (mTORC1) signaling is crucial for translational control involved in long-term memory and in late long-term potentiation (LTP). This is well described in principal glutamatergic pyramidal cells but poorly understood in GABAergic inhibitory interneurons.
<>Here, we show that mTORC1 activity in somatostatin interneurons, a major subclass of GABAergic cells, is important to modulate long-term memory strength and precision. Furthermore, mTORC1 was necessary for learning-induced persistent LTP at excitatory inputs of somatostatin interneurons that depends on type I metabotropic glutamatergic receptors in the hippocampus. This effect was consistent with a newly described role of these interneurons in the modulation of LTP at Schaffer collateral synapses onto pyramidal cells."[41]

[E2] mTORC2 is crucial for memory consolidation.

"<>To be become long-lasting, short-term memories must be transformed into more permanent forms. mTORC2 has now been found to be crucial for the molecular reorganization of the cytoskeleton needed for memory consolidation."
"<>systemic injection of a small molecule that increases mTORC2 activity not only facilitated L-LTP in the slice but also enhanced long-term memory formation in wild-type mice. By both increasing and decreasing mTORC2 function, Huang et al. provide compelling evidence that mTORC2, acting through actin polymerization, is important in formation of stable memories. They showed that this mechanism was conserved in both flies and mice. Taken together, these findings raise the question of whether targeting mTORC2 might similarly enhance memory and other cognitive functions in humans. Given that mTORC2 disruption is implicated in many human diseases associated with cognitive dysfunction, the present study offers a tantalizing prospect for future therapeutic avenues."[42]

[F] 4EBP1 expression is decreased following resistance training, which paradoxically suppresses protein synthesis (for a short period of time) which then, as a supposed compensatory mechanism, activates the anabolic cascade of mTOR.

"<>In summary, these data show that during endurance-type exercise, 4EBP1 dephosphorylation occurs to a greater extent at high vs. low exercise intensities, whereas eEF2 phosphorylation increases similarly at all exercise intensities, which may be explained by a selective increase in type I myofibers. Others have surmised that the suppression of skeletal muscle protein synthesis during exercise may be part of the

stimulus by which protein synthesis is enhanced after exercise. Given that the intensity of exercise training is important for subsequent adaptive responses of skeletal muscle, the putative higher blunting of protein synthesis by greater 4EBP1 dephosphorylation during high-intensity exercise may be part of the molecular mechanism by which high-intensity exercise training promotes greater adaptations than low-intensity training."[43]

[F2] An early rise in AMPK post-exercise reduces protein synthesis but this effect is temporary.

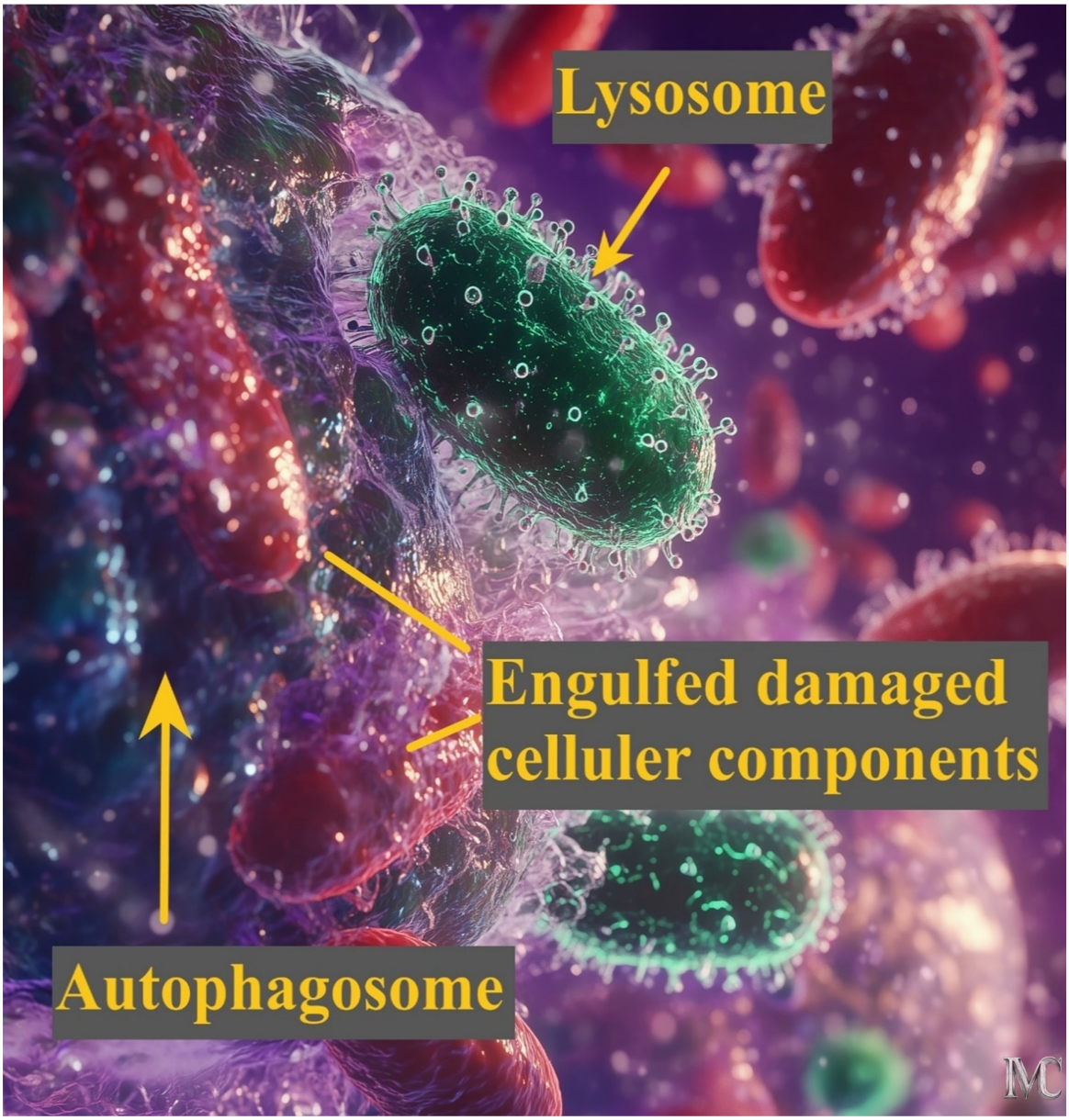
"<>Resistance exercise is a potent stimulator of muscle protein synthesis and muscle cell growth, with the increase in protein synthesis being detected within 2-3 h post-exercise and remaining elevated for up to 48 h. However, during exercise, muscle protein synthesis is inhibited. An increase in AMP-activated protein kinase (AMPK) activity has recently been shown to decrease mammalian target of rapamycin (mTOR) signalling to key regulators of translation initiation. We hypothesized that the cellular mechanism for the inhibition of muscle protein synthesis during an acute bout of resistance exercise in humans would be associated with an activation of AMPK
and an inhibition of downstream components of the mTOR pathway (4E-BP1 and S6K1).
<>We studied 11 subjects (seven men, four women) before, during, and for 2 h following a bout of resistance exercise. Muscle biopsy specimens were collected at each time point from the vastus lateralis. We utilized immunoprecipitation and immunoblotting methods to measure muscle AMPKalpha2 activity, and mTOR-associated upstream and downstream signalling proteins, and stable isotope techniques to measure muscle fractional protein synthetic rate (FSR).
<>AMPKalpha2 activity (pmol min(-1) (mg protein)(-1)) at baseline was 1.7 +/- 0.3, increased immediately post-exercise (3.0 +/- 0.6), and remained elevated at 1 h post-exercise ($P < 0.05$). Muscle FSR decreased during exercise and was significantly increased at 1 and 2 h post-exercise ($P < 0.05$). Phosphorylation of 4E-BP1 at Thr37/46 was significantly reduced immediately post-exercise ($P < 0.05$). We conclude that AMPK activation and a reduced phosphorylation of 4E-BP1 may contribute to the inhibition of muscle protein synthesis during resistance exercise. However, by 1-2 h post-exercise, muscle protein synthesis increased in association with an activation of protein kinase B, mTOR, S6K1 and eEF2."[44]

5' Adenosine Monophosphate Activated Protein Kinase (AMPK): Isoform Alpha 1/2

An energy sensing enzyme that rises in the body under caloric restriction, ergogenic chemical use, or high intensity / high-volume exercise. It is associated with the initiation of processes such as skeletal muscle and neurological autophagy, exercise-induced angiogenesis, mitochondrial biogenesis, muscle lactate production, glycogen storage, neurogenesis, & neuroprotection.
Thus far, AMPK has been thought of as antagonistic of TOR (mTOR), and therefore a suppressor of myogenesis, but this is not the case if protein consumption is high, and

exercise is performed frequently, for new research has shown that certain isoforms of AMPK actually promote myogenesis. This means that the unspoken belief that one should not engage in too much cardio if they are focused solely on muscle growth is quite illogical.

AMPK Subsection: Autophagy



Autophagy is a catabolic process where certain intracellular components are broken down, such as damaged mitochondria which often produce an unnecessary amount of ROS. Phagophores are formed and released through the Endoplasmic Reticulum, they

locate cellular material marked for autophagy and begin to engulf it, after engulfment is complete this is considered the formation of the Autophagosome, after which point a lysosome molecule travels to the Autophagosome to merge with it (activate it), forming an Autolysosome, which activate its programmed digestive process through enzyme release, wherein the cellular components contained within the Autophagosome are digested and their breakdown products are reused for protein synthesis or energy production.

Autophagy is a complex term that may be confused with phagocytosis, a process wherein primarily large extracellular material such as bacteria, dead tissue, or neurological molecular trash (amyloid-beta molecules) are digested by phagocytic cells (macrophages, neutrophils). Autophagy involves only intracellular component breakdown. Mitophagy describes the selective breakdown of damaged intracellular mitochondria. Autophagy also should not be confused with proteolysis, where muscle proteins are broken down to provide the body with nutrients during starvation or exposure to stress hormones, although the two processes often occur simultaneously such as during starvation, or intense exercise.

[1] Muscle autophagy is required for optimal muscle health. The accumulation of autophagosomes in muscle tissue in dystrophic muscle is a sign of impaired autophagy flux. This may be due to increased mTOR expression, or reduced AMPK expression, thereby disturbing the natural progression of autophagy. Endurance exercise or high volume aerobic exercise would theoretically counteract this perturbation by promoting efficient autophagy through lysosomal biogenesis, whereas high load-low volume (strength training) exercise would exacerbate this issue, thus explaining why classical resistance training in the elderly displays limited benefits beyond stem cell availability. Interestingly, the ketone BHB has been shown to prevent autophagosome accumulation in neurons[1.2], which possibly translates to muscle tissue.

“<>Skeletal muscle is comprised of highly organized myofibers containing aligned contractile units called sarcomeres. Through the rhythmic activity of the actin filaments and myosin motor proteins within the sarcomeres, skeletal muscle provides the force for movement and support required by the body. Daily movements, accentuated during physical activity, produce high amounts of reactive oxygen species, which can damage cellular components. Moreover, skeletal muscle comprises roughly 40% of whole body lean mass, thereby providing a tissue source for amino acids that can be used in times of stress or starvation.
<>Thus, skeletal muscle needs an efficient method of not only recycling damaged or aged organelles and accumulated protein aggregates, but also breaking down protein to meet the energy demands of the body. Macroautophagy (herein autophagy) represents the physiological process skeletal muscle utilizes to transport cytoplasm, organelles, and proteins to the lysosome for degradation. Autophagy is vital for removing old and damaged cellular components, breaking down undedicated nutrient stores, and remodeling cellular architecture.

<>Recently, examination of various skeletal muscle diseases causing atrophy and dystrophy has discovered an interesting common feature; the buildup of autophagosomes within myofibers. This striking feature of diseased skeletal muscle underlies the importance of autophagy in proper skeletal muscle function."[44.1]

[1.2] "<>Glucose is the major energy substrate in brain, however, during ketogenesis induced by starvation or prolonged hypoglycemia, the ketone bodies (KB), acetoacetate and β-hydroxybutyrate (BHB) can substitute for glucose. KB improve neuronal survival in diverse injury models, but the mechanisms by which KB prevent neuronal damage are still not well understood. In the present study we have investigated whether protection by the D isomer of BHB (D-BHB) against neuronal death induced by glucose deprivation (GD), is related to autophagy.
<>Autophagy is a lysosomal-dependent degradation process activated during nutritional stress, which leads to the digestion of damaged proteins and organelles providing energy for cell survival. Results show that autophagy is activated in cortical cultured neurons during GD, as indicated by the increase in the levels of the lipidated form of the microtubule associated protein light chain 3 (LC3-II), and the number of autophagic vesicles. At early phases of glucose reintroduction (GR), the levels of p62 declined suggesting that the degradation of the autophagolysosomal content takes place at this time.
<>In cultures exposed to GD and GR in the presence of D-BHB, the levels of LC3-II and p62 rapidly declined and remained low during GR, suggesting that the KB stimulates the autophagic flux preventing autophagosome accumulation and improving neuronal survival."[44.1.1]

[2] HIT cardiovascular exercise (70-75% predicted Max HR) promotes systemic autophagy. Whether this is because of enhanced AMPK expression, improved blood flow, epigenetic changes brought on by catecholamines, ketones, or a combination of factors is up for debate.

"<>We recently identified physical exercise as a newly defined inducer of autophagy in vivo. Exercise induced autophagy in multiple organs involved in metabolic regulation, such as muscle, liver, pancreas and adipose tissue. To study the physiological role of exercise-induced autophagy, we generated mice with a knock-in nonphosphorylatable mutation in BCL2 (Thr69Ala, Ser70Ala and Ser84Ala) (BCL2 AAA) that are defective in exercise- and starvation-induced autophagy but not in basal autophagy.
<>We found that BCL2 AAA mice could not run on a treadmill as long as wild-type mice, and did not undergo exercise-mediated increases in skeletal glucose muscle uptake. Unlike wild-type mice, the BCL2 AAA mice failed to reverse high-fat diet-induced glucose intolerance after 8 weeks of exercise training, possibly due to defects in signaling pathways that regulate muscle glucose uptake and metabolism during exercise.
<>Together, these findings suggested a hitherto unknown important role of autophagy in mediating exercise-induced metabolic benefits. In the present addendum, we show that treadmill exercise also induces autophagy in the cerebral cortex of adult mice. This

observation raises the intriguing question of whether autophagy may in part mediate the beneficial effects of exercise in neurodegeneration, adult neurogenesis and improved cognitive function."[44.1.2]

[3] Skeletal Muscle Autophagy is clearly necessary for functioning mitochondria, but more interesting a deficiency in this process results in decreased muscle force [See: Anti-Inflammation Cycle Supplementation: Caffeine, Other Hormones (Non-Androgenic): [C3]].

"<>The ubiquitin-proteasome and autophagy-lysosome pathways are the two major routes for protein and organelle clearance. In skeletal muscle, both systems are under FoxO regulation and their excessive activation induces severe muscle loss. Although altered autophagy has been observed in various myopathies, the specific role of autophagy in skeletal muscle has not been determined by loss-of-function approaches. Here, we report that muscle-specific deletion of a crucial autophagy gene, Atg7, resulted in profound muscle atrophy and age-dependent decrease in force. Atg7 null muscles showed accumulation of abnormal mitochondria, sarcoplasmic reticulum distension, disorganization of sarcomere, and formation of aberrant concentric membranous structures.
<>Autophagy inhibition exacerbated muscle loss during denervation and fasting. Thus, autophagy flux is important to preserve muscle mass and to maintain myofiber integrity. Our results suggest that inhibition/alteration of autophagy can contribute to myofiber degeneration and weakness in muscle disorders characterized by accumulation of abnormal mitochondria and inclusions."[44.2]

[4] Excessive Autophagy is a concern, wherein too many intracellular components are broken down and recycled leading ultimately to cell death.

"<>Aims: To determine the extent to which autophagy contributes to neuronal death in cerebral hypoxia and ischemia.
<>Methods: We performed immunocytochemistry, western blot, cell viability assay, and electron microscopy to analyze autophagy activities in vitro and in vivo.
<>Results: In both primary cortical neurons and SH-SY5Y cells exposed to oxygen and glucose deprivation (OGD)for 6 h and reperfusion (RP) for 24, 48, and 72 h, respectively, an increase of autophagy was observed as determined by the increased ratio of LC3-II to LC3-I and Beclin-1 (BECN1) expression. Using Fluoro-Jade C and monodansylcadaverine double-staining, and electron microscopy we found the increment in autophagy after OGD/RP was accompanied by increased autophagic cell death, and this increased cell death was inhibited by the specific autophagy inhibitor, 3-methyladenine. The presence of large autolysosomes and numerous autophagosomes in cortical neurons were confirmed by electron microscopy. Autophagy activities were increased dramatically in the ischemic brains 3-7 days postinjury from a rat model of neonatal cerebral hypoxia/ischemia as shown by increased punctate LC3 staining and BECN1 expression."[44.3]

[A] AMPK promotes angiogenesis.

"<>AMP-activated protein kinase (AMPK) is a stress-activated protein kinase that is regulated by hypoxia and other cellular stresses that result in diminished cellular ATP levels. Here, we investigated whether AMPK signaling in endothelial cells has a role in regulating angiogenesis. Hypoxia induced the activating phosphorylation of AMPK in human umbilical vein endothelial cells (HUVECs), and AMPK activation was required for the maintenance of pro-angiogenic Akt signaling under these conditions. Suppression of AMPK signaling inhibited both HUVEC migration to VEGF and in vitro differentiation into tube-like structures in hypoxic, but not normoxic cultures. Dominant-negative AMPK also inhibited in vivo angiogenesis in Matrigel plugs that were implanted subcutaneously in mice.
<>These data identify AMPK signaling as a new regulator of angiogenesis that is specifically required for endothelial cell migration and differentiation under conditions of hypoxia. As such, endothelial AMPK signaling may be a critical determinant of blood vessel recruitment to tissues that are subjected to ischemic stress."[45]

[B] AMPK a1 isoform but not a2 isoform promotes myogenesis.
"<>The link between AMP-activated protein kinase (AMPK) and myogenesis remains poorly defined. AMPK has two catalytic α subunits, α1 and α2. We postulated that AMPK promotes myogenesis in an isoform-specific manner. Primary myoblasts were prepared from AMPK knockout (KO) mice and AMPK conditional KO mice, and knockout of the α1 but not the α2 subunit resulted in downregulation of myogenin and reduced myogenesis. Myogenin expression and myogenesis were nearly abolished in the absence of both AMPKα1 and AMPKα2, while enhanced AMPK activity promoted myogenesis and myotube formation.
<>The AMPKα1-specific effect on myogenesis was likely due to the dominant expression of α1 in myoblasts. These results were confirmed in C2C12 cells. To further evaluate the necessity of the AMPKα1 subunit for myogenesis in vivo, we prepared both DsRed AMPKα1 knockout myoblasts and enhanced green fluorescent protein (EGFP) wild-type myoblasts, which were cotransplanted into tibialis anterior muscle. A number of green fluorescent muscle fibers were observed, showing the fusion of engrafted wild-type myoblasts with muscle fibers; on the other hand, very few or no red muscle fibers were observed, indicating the absence of myogenic capacity of AMPKα1 knockout myoblasts. In summary, these results indicate that AMPK activity promotes myogenesis through a mechanism mediated by AMPKα1."[46]

[C] AMPK is essential for muscle proteolysis by promoting alanine release (gluconeogenesis) from skeletal muscle, but a lack of AMPK results in myopathy (weakness, mitochondrial abnormalities) due to a lack of autophagy and accumulation of dysfunctional intracellular components.

"<>The AMP-activated protein kinase (AMPK) activates autophagy, but its role in aging and fasting-induced muscle function has not been defined. Here we report that fasting

mice lacking skeletal muscle AMPK (AMPK-MKO) results in hypoglycemia and hyperketosis. This is not due to defective fatty acid oxidation, but instead is related to a block in muscle proteolysis that leads to reduced circulating levels of alanine, an essential amino acid required for gluconeogenesis. Markers of muscle autophagy including phosphorylation of Ulk1 Ser555 and Ser757 and aggregation of RFP-LC3 puncta are impaired.
<>Consistent with impaired autophagy, aged AMPK-MKO mice possess a significant myopathy characterized by reduced muscle function, mitochondrial disease, and accumulation of the autophagy/mitophagy proteins p62 and Parkin. These findings establish an essential requirement for skeletal muscle AMPK-mediated autophagy in preserving blood glucose levels during prolonged fasting as well as maintaining muscle integrity and mitochondrial function during aging."[47]

[D] AMPK inhibits TGF-b. [See: Muscle Fibrosis, Anti-Inflammation Supplementation: Caffeine].

"<>Adenosine monophosphate-activated protein kinase (AMPK) acts as a fuel gauge that maintains energy homeostasis in both normal and cancerous cells, and has emerged as a tumor suppressor. The present study aims to delineate the functional relationship between AMPK and transforming growth factor beta (TGF-β). Our results showed that expression of liver kinase B1 (LKB1), an upstream kinase of AMPK, impeded TGF-β-induced Smad phosphorylation and their transcriptional activity in breast cancer cells, whereas knockdown of LKB1 or AMPKα1 subunit by short hairpin RNA (shRNA) enhanced the effect of TGF-β. Furthermore, AMPK activation reduced the promoter activity of TGF-β1. In accordance, type 2 diabetic patients taking metformin displayed a trend of reduction of serum TGF-β1, as compared with those without metformin.
<>A significant reduction of serum TGF-β1 was found in mice after treatment with metformin. These results suggest that AMPK inhibits the transcription of TGF-β1, leading to reduction of its concentration in serum. Finally, metformin suppressed epithelial-to-mesenchymal transition of mammary epithelial cells. Taken together, our study demonstrates that AMPK exerts multiple actions on TGF-β signaling and supports that AMPK can serve as a therapeutic drug target for breast cancer."[47.1]

[E] AMPK is not always antagonistic to mTOR expression, as both are stimulated by amino acids (aa), and exercise.

"<>Strikingly, AMPK responded acutely and within 1 min to aa, and its activation was independent of the other aa-responsive components mTORC2, PI3K and mTORC1. This suggests aa as novel metabolic activators of AMPK. This finding was unexpected because AMPK is mainly considered to be activated by stress and starvation conditions, including aa withdrawal although there is conflicting data. This may in turn imply that aa exert an inhibitory effect on AMPK, which has indeed been suggested by several studies. It should be noted though that all these studies observed AMPK phosphorylation at the

earliest at 15 min post aa addition. At this time point we also observed AMPK repression, and this is why the earlier studies may have missed the early AMPK inducibility by aa. <>Our data suggest that activation of the CaMKKβ-AMPK axis by aa does not inhibit mTORC1, but sustains ULK1 activity and autophagy. Likewise, c-Jun, reported to respond to AMPK56 and to inhibit autophagy, was phosphorylated upon aa readdition, and hyperphosphorylated when CaMKKβ was inhibited. Aa readdition activates mTORC1-dependent translation, which is generally perceived as being associated with an inhibition of autophagy. Why may cells activate autophagy in response to nutrient readdition? It has been noted recently that activation of biosynthetic pathways may require autophagy for several reasons. Firstly, increased protein synthesis inevitably also increases the amount of misfolded proteins, and autophagy contributes to their clearance. <>Secondly, the upregulation of biosynthetic processes requires increased amounts of metabolite intermediates, which are provided by autophagy as well. Consistent with this, a previous study described active autophagy in the context of active mTORC1 signalling."[47.2]

[F] AMPK enhances lactate accumulation during muscle contraction. [See: Lactic Acid Training].

"<>The AMP-activated protein kinase (AMPK) is a cellular sensor of energetics and when activated in skeletal muscle during contraction can impart changes in skeletal muscle metabolism. Therapeutics that selectively activate AMPK have been developed to lower glucose levels through increased glucose disposal rates as an approach to abrogate the hyperglycemic state of diabetes; however, the metabolic fate of glucose following AMPK activation remains unclear. We have used a combination of in vivo evaluation of glucose homeostasis and ex vivo skeletal muscle incubation to systematically evaluate metabolism following pharmacological activation of AMPK with PF-739, comparing this with AMPK activation through sustained intermittent electrical stimulation of contraction.
<>These methods to activate AMPK result in increased glucose uptake but divergent metabolism of glucose: pharmacological activation results in increased glycogen accumulation while contraction-induced glucose uptake results in increased lactate formation and glucose oxidation. These results provide additional evidence to support a role for AMPK in control of skeletal muscle metabolism and additional insight into the potential for AMPK stimulation with small molecule direct activators."[47.3]

[G] AMPK a1 Isoform is necessary for muscle regeneration through satellite cell activation following injury and is found to have decreased activity in obese individuals. This does not necessarily mean obesity prevents myogenesis, as many of the strongest humans on earth are overweight, it means the benefits of adipose tissue on myogenesis dissipate after a certain amount of adipogenesis occurs in the body. I would hypothesize 25% body fat is the threshold.

"<>Obesity is increasing rapidly worldwide and is accompanied by many complications, including impaired muscle regeneration. The obese condition is known to inhibit AMPK activity in multiple tissues. We hypothesized that the loss of AMPK activity is a major reason for hampered muscle regeneration in obese subjects. We found that obesity inhibits AMPK activity in regenerating muscle, which was associated with impeded satellite cell activation and impaired muscle regeneration. <>To test the mediatory role of AMPKα1, we knocked out AMPKα1 and found that both proliferation and differentiation of satellite cells are reduced after injury and that muscle regeneration is severely impeded, reminiscent of hampered muscle regeneration seen in obese subjects. Transplanted satellite cells with AMPKα1 deficiency had severely impaired myogenic capacity in regenerating muscle fibers. We also found that attenuated muscle regeneration in obese mice is rescued by AICAR, a drug that specifically activates AMPK, but AICAR treatment failed to improve muscle regeneration in obese mice with satellite cell–specific AMPKα1 knockout, demonstrating the importance of AMPKα1 in satellite cell activation and muscle regeneration.
<>In summary, AMPKα1 is a key mediator linking obesity and impaired muscle regeneration, providing a convenient drug target to facilitate muscle regeneration in obese populations."[47.4]

Focal Adhesion Kinase (FAK)

[A] FAK is required for the early stages of muscle regeneration. [See: Pro-Inflammation Modalities: Deep-Tissue Massage].

"<>There is evidence that FAK is necessary for proper myoblast fusion. FAK has been shown to be expressed at higher levels in myotubes compared to myoblasts. Satellite cell-specific FAK knock out mice had a fourfold decrease in regenerating fibers 3 days after BaCl2-induced injury and inhibition of FAK by its FAT domain or siRNA prevented myoblast fusion."[48]

[B] FAK promotes costamerogenesis, which leads to the enhancement of muscle force production.

"<>A central question in muscle biology is how costameres are formed and become aligned with underlying myofibrils in mature tissues. Costameres are composed of focal adhesion proteins, including vinculin and paxillin, and anchor myofibril Z-bands to the sarcolemma. In the present study, we investigated the process of costamere formation ("costamerogenesis") in differentiating primary mouse myoblasts. Using vinculin and paxillin as costameric markers, we found that two additional focal adhesion components, alpha5beta1 integrin and focal adhesion kinase (FAK), are associated with costameres. <>We have characterized costamerogenesis as occurring in three distinct stages based on the organizational pattern of these costameric proteins. We show that both costamerogenesis and myofibrillogenesis are initiated at sites of membrane contacts with the extracellular matrix and that their maturation is tightly coupled. To test the

importance of FAK signaling in these processes, we analyzed cells expressing a dominant negative form of FAK (dnFAK). When cells expressing dnFAK were induced to differentiate, both costamerogenesis and myofibrillogenesis were disrupted although the expression of constituent proteins was not inhibited.
<>Likewise, inhibiting FAK activity by reducing FAK levels using an siRNA approach also resulted in an inhibition of costamerogenesis and myofibrillogenesis. The relationship between costamere and myofibril formation was tested further by treating myotube cultures with potassium or tetrodotoxin to block contraction and disrupt myofibril organization. This also resulted in inhibition of costamere maturation. We present a model of costamerogenesis whereby signaling through FAK is essential for both normal costamerogenesis and normal myofibrillogenesis which are tightly coupled during skeletal myogenesis."[49]

[C] FAK enhances neuritogenesis.

"<>The focal adhesion kinase (FAK) is a non-receptor tyrosine kinase abundantly expressed in the mammalian brain and highly enriched in neuronal growth cones. Inhibitory and facilitatory activities of FAK on neuronal growth have been reported and its role in neuritic outgrowth remains controversial. Unlike other tyrosine kinases, such as the neurotrophin receptors regulating neuronal growth and plasticity, the relevance of FAK for learning and memory in vivo has not been clearly defined yet. A comprehensive study aimed at determining the role of FAK in neuronal growth, neurotransmitter release and synaptic plasticity in hippocampal neurons and in hippocampus-dependent learning and memory was therefore undertaken using the mouse model. Gain- and loss-of-function experiments indicated that FAK is a critical regulator of hippocampal cell morphology. <>FAK mediated neurotrophin-induced neuritic outgrowth and FAK inhibition affected both miniature excitatory postsynaptic potentials and activity-dependent hippocampal long-term potentiation prompting us to explore the possible role of FAK in spatial learning and memory in vivo. Our data indicate that FAK has a growth-promoting effect, is importantly involved in the regulation of the synaptic function and mediates in vivo hippocampus-dependent spatial learning and memory."[50]

cAMP Response Element Binding Protein (CREB)

CREB is an upstream factor of MAPK's that activates in damaged muscle tissue to promote the earliest stage myogenesis.

"<>The cAMP response element binding protein (CREB) plays key roles in differentiation of embryonic skeletal muscle progenitors and survival of adult skeletal muscle. However, little is known about the physiologic signals that activate CREB in normal muscle. Here we show that CREB phosphorylation and target genes are induced after acute muscle injury and during regeneration due to genetic mutation. <>Activated CREB localizes to both myogenic precursor cells and newly regenerating myofibers within regenerating areas. Moreover, we found that signals from damaged skeletal

muscle tissue induce CREB phosphorylation and target gene expression in primary mouse myoblasts. An activated CREB mutant (CREBY134F) potentiates myoblast proliferation as well as expression of early myogenic transcription factors in cultured primary myocytes.
<>Consistently, activated CREB-YF promotes myoblast proliferation after acute muscle injury in vivo and enhances muscle regeneration in dystrophic mdx mice. Our findings reveal a new physiologic function for CREB in contributing to skeletal muscle regeneration."[50.1]

Mitogen-Activated Protein Kinases (MAPKs)

MAPKs are protein kinases and downstream activators of ERK1/2 and JNK that stimulate pro-inflammatory cytokine release and growth processes in the body. MAPKs associate with high load training.

"<>Power is critical to muscle performance, specifically in athletic populations. Mitogen-activated protein kinase (MAPK) pathways (extracellular signal-regulated protein kinase (ERK 1/2), p38, and c-Jun NH(2)-terminal kinase (JNK)) are intracellular signal transduction mechanisms that partially regulate exercise-induced skeletal muscle alterations. These pathways are highly responsive to exercise, but their reaction to high power, multi-joint resistance exercise is yet to be examined. <>Nine weightlifting-trained men performed 15 sets of three repetitions of a dynamic clean pull exercise at 85% of their one repetition maximum. Vastus lateralis biopsies were obtained prior to (pre) and after the 8th (mid) and 15th set (post) of exercise. Three subjects returned to serve as non-exercising controls for a similar sequence of biopsies (CON).
<>The ratio of phosphorylated MAPK to total MAPK increased significantly for p38 (3.0 fold, $p < 0.05$) and JNK (2.4 fold, $p < 0.05$) by the mid biopsy. ERK 1/2 phosphorylation followed a similar trend (2.3 fold) ($p = 0.052$). The ratio of phosphorylation to total MAPK did not differ from mid to post biopsy. None of the pathways were phosphorylated above resting in the CON condition ($p > 0.05$), and thus the biopsy procedure itself did not account for the entire increase in MAPK phosphorylation during EX. These data indicate MAPK pathways are activated early and remain elevated throughout the duration of high power resistance exercise. These findings help describe the mechanisms partially responsible for chronic adaptations in response to high intensity, high power resistance training in humans."[51.0]

Extracellular Signal Regulated Kinase 1/2 (ERK1/2)

[A] ERK1/2 Promotes slow twitch fiber growth.

"<>Mitogen-activated protein kinase (MAPK) signaling consists of an array of successively acting kinases. The extracellular signal-regulated kinases 1/2 (ERK1/2) are major components of the greater MAPK cascade that transduce growth factor signaling at

the cell membrane. Here we investigated ERK1/2 signaling in skeletal muscle homeostasis and disease. Using mouse genetics, we observed that the muscle-specific expression of a constitutively active MEK1 mutant promotes greater ERK1/2 signaling that mediates fiber-type switching to a slow, oxidative phenotype with type I myosin heavy chain expression. Using a conditional and temporally regulated Cre strategy as well as Mapk1 (ERK2) and Mapk3 (ERK1) genetically targeted mice, MEK1-ERK2 signaling was shown to underlie this fast-to-slow fiber type switching in adult skeletal muscle as well as during development. Physiologic assessment of these activated MEK1-ERK1/2 mice showed enhanced metabolic activity and oxygen consumption with greater muscle fatigue resistance.
<>Moreover, induction of MEK1-ERK1/2 signaling increased dystrophin and utrophin protein expression in a mouse model of limb-girdle muscle dystrophy and protected myofibers from damage. In summary, sustained MEK1-ERK1/2 activity in skeletal muscle produces a fast-to-slow fiber-type switch that protects from muscular dystrophy, suggesting a therapeutic approach to enhance the metabolic effectiveness of muscle and protect from dystrophic disease."[51]

[B] ERK1/2 promotes myogenic proliferation.

"<>Skeletal muscle satellite cells, which are found between the muscle fiber and the basal lamina, remain quiescent and undifferentiated unless stimulated to remodel skeletal muscle or repair injured skeletal muscle tissue. Quiescent satellite cells express c-met and fibroblast growth factor receptors (FGFR) 1 and 4, suggesting these receptors are involved in maintaining the undifferentiated quiescent state or involved in satellite cell activation. Although the signaling pathways involved are poorly understood, the mitogen activated protein kinase (MAPK) cascade has been implicated in the regulation of skeletal muscle growth and differentiation by FGFs. In this study, we investigated if activation of the Raf-MKK1/2-ERK1/2 signaling cascade plays a role in FGF-dependent repression of differentiation and proliferation of MM14 cells, a skeletal muscle satellite cell line.
<>Inactivation of the Raf-MKK1/2-ERK1/2 pathway in myoblasts through the overexpression of dominant negative mutants of Raf-1 blocks ERK1/2 activity and prevents myoblast proliferation. Additionally, inhibition of MKK1/2 by treatment with pharmacological inhibitors also blocks FGF-mediated stimulation of ERK1/2 and blocks the G1 to S phase transition of myoblasts. Unexpectedly, we found that inactivation of the Raf-ERK pathway does not activate a muscle reporter, nor does inactivation of this pathway promote myogenic differentiation. We conclude that FGF-stimulated ERK1/2 signaling is required during the G1 phase of the cell cycle for commitment of myoblasts to DNA synthesis but is not required for mitosis once cells have entered the S-phase. Moreover, ERK1/2 signaling is not required either to repress differentiation, to promote skeletal muscle gene expression, or to promote myoblast fusion."[52]

[C] ERK1/2 is essential for neurite outgrowth.

"<>Mitogen-activated protein kinase (MAPK) pathways are central signaling elements, which translate and integrate stimuli from cell surface receptors into cytoplasmic and transcriptional responses. Here, we systematically compare the role of MAPKs in the nerve growth factor-induced long-term differentiation of PC12 cells and show the persistent nuclear and dose-dependent cytoplasmic activation of extracellular signal-regulated kinases 1 and 2 (ERK1/2) and the increasing nuclear and cytoplasmic activation of c-Jun N-terminal kinases (JNKs). Inhibition of ERK1/2 and JNKs significantly reduced neurite outgrowth.
<>Both synergistically controlled the expression of c-Jun, the induction and/or phosphorylation of neurofilament, and the phosphorylation of Elk-1. JNKs alone were responsible for the phosphorylation of c-Jun and activating transcription factor 2 as well as for the expression of MAPK phosphatase 1. In contrast, p38alpha was only transiently activated and marginally involved in these processes.
<>Thus, JNKs and ERK1/2 accomplish differentiation by signaling in parallel cascades that converge only at the target level."[53]

c-Jun N-terminal kinase (JNK)

[A] JNK is essential for muscle differentiation.

"<>Previous studies on skeletal muscle differentiation showed that myogenesis is regulated by extracellular signal-regulated kinases (ERK-1/-2) and p38 mitogen activated kinase (MAPK) pathways.
<>Present study shows that c-Jun NH2-terminal protein kinase (JNK) activities were up regulated during skeletal muscle differentiation in rat skeletal muscle L6E9 cells, as determined by Western immunoblot of differentiating cells probed with anti-phospho-JNK antibody. Inhibition of JNK activities by JNK inhibitor II drastically inhibited differentiation as determined by decreased myosin, myogenin expression and creatine kinase activity. The inhibition of the differentiation was regulated by apoptosis as determined by the detection of poly(ADP-ribose) polymerase (PARP) cleavage, terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) positive cells when JNK activities were inhibited. Apoptosis was accompanied by marked expression and activation of c-Jun and p53 transcription factors.
<>Taken together, our results indicate that basal JNK activities are essential for regulating skeletal muscle differentiation, and inhibition of JNK activation affects myogenesis by apoptosis dependent on c-Jun and p53 transcription factors."[53.1]

[B] JNK suppresses SMAD-2 / Myostatin expression.

"<>While JNK is known to have several molecular targets, we identify SMAD2 as a novel exercise-activated JNK substrate. The discovery that JNK inhibits SMAD2 in muscle has important clinical implications, as SMAD2 is a downstream effector of myostatin- a TGFβ superfamily ligand. Our data clearly show that JNK activation through multiple means, including pharmacological treatment, genetic manipulation, or

muscle contraction leads to phosphorylation of the transcription factor SMAD2 at specific linker region residues. In turn, we provide evidence that JNK-mediated SMAD2 phosphorylation has an inhibitory effect on SMAD2 transcriptional activity and nuclear translocation. We also observed an inhibition of SMAD3 translocation to the nucleus in myocytes with JNK activation. The precise mechanisms for the inhibitory effect of JNK on SMAD3 have yet to be elucidated. The inhibitory effect of JNK on SMAD3 may be due to phosphorylation of SMAD3 by JNK on a yet undetermined residue(s), or and indirect effect via complex formation with SMAD2. <>However, it has previously been demonstrated that both SMAD2 and SMAD3 are necessary for the effects of TGFβ/myostatin on muscle mass. Myostatin acts as a molecular brake that prevents muscle hypertrophy, while its inhibition allows for muscle growth. Loss-of-function mutations in the myostatin gene, or inhibition of myostatin function via pharmacological antagonism, results in clinically significant increases in muscle mass in humans and animals. Therefore, myostatin receptor antagonism is being explored as a treatment for muscle wasting diseases, such as cachexia and sarcopenia.
<>Our work identifying JNK as a novel myostatin inhibitor provides a mechanism for our observation that mJNKKO mice have severely impaired overload-induced hypertrophy. Furthermore, we identify JNK activation as an alternative strategy for clinical myostatin inhibition."[53.2]

p38 Mitogen-Activated Protein Kinase

p38 is necessary for both skeletal muscle proliferation and differentiation, through the activation of satellite cells.

"<>The consequences of p38α/β inhibition are manifested as a failure to differentiate (a phenotype that is observed when p38α/β is inhibited in the MM14, C2C12, and L6/L8 cell lines) and a failure to proliferate in both MM14 cells and satellite cells, a novel observation. The inhibition of proliferation and the block to differentiation both occur when p38α/β activity is inhibited in the G1 phase of the cell cycle. Targets of the p38α/β MAPKs that mediate these events are unidentified. Although a significant body of data has shown that MEF2A and MEF2C are substrates of p38α and p38β2, satellite cells do not express detectable MEF2 transcripts until 96 h after myofiber isolation, suggesting that these are unlikely p38α/β targets for satellite cell activation or proliferation.
<>Other known substrates of p38α/β include transcription factors (Max and ATF2), kinases (MAPKAP kinase 2 and 3), and phospholipase A2 (Lewis et al., 1998). In proliferating MM14 cells, manipulation of p38α/β activity by FGF removal or by SB203580 addition has no significant effect on ATF2-dependent transcription. However, in differentiated cells, ATF2-dependent transcription is SB203580 and FGF-2 sensitive. This suggests that p38α/β MAPKs act upon different substrates in proliferating and differentiating cells. A similar observation was noted for MM14 cells where differential activation of the ERK1/2 pathway occurred in cells committed to S-phase as compared with cells committed to terminal differentiation. These reports provide supporting

evidence for differences in signaling pathways that are dependent on the phenotypic state of skeletal muscle cells.
<>When further analyzed for differences in substrate specificity, we found that the majority of p38α/β substrates were different in proliferating versus differentiated cells. Thus, the observation that p38α/β MAPKs are required for both proliferation and differentiation could be explained by differential substrate accessibility imposed by commitment of the cell to S-phase or to terminal differentiation. A better understanding of the roles of p38α/β MAPKs in these events will require identification of substrates specific for cells committed to proliferate and differentiate."[53.3]

B-Catenin

[A] B-Catenin promotes myogenic differentiation, but when chronically active causes premature differentiation of muscle fibers, resulting in blunted hypertrophy.
[See: Anti-Inflammation Cycle Supplementation: Lithium].

"<>Skeletal muscle regeneration relies on a pool of resident muscle stem cells called satellite cells (MuSCs). Following injury-induced destruction of the myofibers, quiescent MuSCs are activated and generate transient amplifying progenitors (myoblasts) that will fuse to form new myofibers.
<>Here, we focus on the canonical Wnt signaling pathway and find that either conditional β-catenin disruption or activation in adult MuSCs results in perturbation of muscle regeneration. Using both in vivo and in vitro approaches, we observed that myoblasts lacking β-catenin show delayed differentiation, whereas myoblasts with constitutively active β-catenin undergo precocious growth arrest and differentiation. Transcriptome analysis further demonstrated that Wnt/β-catenin signaling interacts with multiple pathways and, more specifically, TGF-β signaling.
<>Indeed, exogenous TGF-β2 stimulation restores the regenerative potential of muscles with targeted β-catenin disruption in MuSCs. We conclude that a precise level of β-catenin activity is essential for regulating the amplification and differentiation of MuSC descendants during adult myogenesis."[53.4]

[B] B-Catenin promotes neural stem cell proliferation and differentiation.

"<>Stem cells undergo differentiation in complex and dynamic environments wherein instructive signals fluctuate on various timescales. Thus, cells must be equipped to properly respond to the timing of signals, for example, to distinguish sustained signaling from transient noise. However, how stem cells respond to dynamic variations in differentiation cues is not well characterized. Here, we use optogenetic activation of β-catenin signaling to probe the dynamic responses of differentiating adult neural stem cells (NSCs).
<>We discover that, while elevated, sustained β-catenin activation sequentially promotes proliferation and differentiation, transient β-catenin induces apoptosis. Genetic perturbations revealed that the neurogenic/apoptotic fate switch was mediated through

cell-cycle regulation by Growth Arrest and DNA Damage 45 gamma (Gadd45γ). Our results thus reveal a role for β-catenin dynamics in NSC fate decisions and may suggest a role for signal timing to minimize cell-fate errors, analogous to kinetic proofreading of stem-cell differentiation."[53.5]

Toll Like Receptors

Toll Like Receptors 2/4 are pro-inflammatory proteins that associate with muscle fiber type, lipid accumulation, & immunity. TL4R's appear to facilitate Fast twitch muscle fiber growth [See: Pro-Inflammation Cycle Dietary Fats: Coconut Oil].

[A] TLR2 is essential for macrophage infiltration.

"<>More recently, in work published in a recent issue of the Journal of Pathology, the role of TLR2 signalling has been investigated in muscle regeneration in response to traumatic injury. Deficiency of TLR2 reduced the number of macrophages in the injured muscle; however, it did not alter the expression pattern of macrophage polarization markers, such as iNOS and CD206.
<>Consequently, regenerating muscle of TLR2-KO mice exhibited delayed clearance of necrotic tissue and impaired restoration of normal muscle architect."[54]

[B] TLR4 may work in concert with TLR2 to repair damaged muscle tissue by mobilizing macrophages.

"<>Macrophages constitute the predominant inflammatory cell type in most forms of skeletal muscle injury, and they release multiple cytokines, chemokines and extracellular proteases that influence satellite cell behavior, extracellular matrix remodeling and various aspects of skeletal muscle repair. In acutely damaged muscle, depletion of macrophages or interference with macrophage recruitment has been found to have detrimental consequences on muscle regeneration. A reduction in the number of macrophages delays the repair process in muscle following acute injury caused by freezing damage. Furthermore, knockout (KO) of chemokine receptor 2 (CCR2) or its ligand, chemokine ligand 2 (CCL2), which is a macrophage chemoattractant, impedes skeletal muscle regeneration following cardiotoxin injection or ischemia.
<>As proof of concept, transplantation of bone-marrow from wild-type mice rescued the defects in macrophage invasion and muscle regeneration in Ccr2-null mice. More recently, in work published in a recent issue of the Journal of Pathology, the role of TLR2 signaling has been investigated in muscle regeneration in response to traumatic injury. Deficiency of TLR2 reduced the number of macrophages in the injured muscle; however, it did not alter the expression pattern of macrophage polarization markers, such as iNOS and CD206. Consequently, regenerating muscle of TLR2-KO mice exhibited delayed clearance of necrotic tissue and impaired restoration of normal muscle architect. In a related study, injection of Bothrops jararacussu snake venom in GA muscles of C3H/HeJ mice that expressed a non-functional TLR4 receptor resulted in persistent muscular

inflammation, with lower numbers of F4/80+ macrophages but increased activity of matrix metalloproteinase-9 and collagen deposition during resolution of injury, compared to C3H/HeN mice, which expressed functional TLR4 receptor, leading to the conjecture that both TLR2 and TLR4 signaling are essential for skeletal muscle repair following acute injury."[54.1]

Matrix Metalloproteinases

Matrix Metalloproteinases (MMP's) are especially important towards preventing muscle fibrosis following muscle injury[1]. MMPs are enzymes that increase in muscle tissue following exercise, especially overload training (ladder training in mice with weight attached to their tails)[2], to facilitate stem cell movement.

MMP's serve the primary purpose of degrading the Extracellular Matrix (ECM), which thereby allows myoblasts to move through damaged muscle tissue to begin repair processes (hypertrophy, hyperplasia). The primary ECM proteins are Collagen and Fibronectin.

The Extracellular Matrix (ECM), for simplicity of understanding, describes the collagenous barriers of muscle tissue. It serves the role of providing structure and support to myotubes, and it is essential for force transmission, as greater muscle fibrosis will result in greater force transmission, until the point in time in which myotubes begin to degenerate or are converted to fibrotic tissue [See: Overtraining].

[1] "<>Skeletal muscle fibers are surrounded by a basement membrane composed predominantly of type IV collagen, laminin, fibronectin and heparan sulfate proteoglycan. Skeletal muscle satellite cells are considered to be a group of quiescent stem cells that are localized between the plasmalemma and the basement membrane of muscle fiber. Satellite cells play an important role in the repair of injured or inflamed muscle. Once satellite cells are activated following traumatic injury, they migrate to the injured site and differentiate to form new myofibers that fuse to each other or fuse to local surviving muscle fibers, contributing to muscle regeneration. It is believed that a key step for muscle regeneration is when satellite cells migrate across the basement membrane to access the injured site; therefore, the degradation of ECM must be a central component for satellite cell migration and regeneration in vivo.
<>MMPs have been shown to play an essential role in the remodeling and maintenance of the ECM in a wide range of normal and pathological tissues in many organs. There is evidence of extensive remodeling of the ECM of muscle satellite cells during regeneration. It seems that MMPs have a different pattern of expression during the course of muscle injury and repair. MMP-2 and MMP-9 are mainly involved in this ECM remodeling of skeletal muscle. MMP-2 is extensively upregulated during the first three days following cryolesion injury and the amount of mRNA for this enzyme was reduced at day 7 post-lesion, whereas MMP-2 mRNA returned to baseline levels in the skeletal muscle regeneration process at 10 days post-lesion. MMP-9 activity is extensively upregulated during the first three days following cardiotoxin injury in tibialis anterior (TA) muscle, whereas after three days following the injury, the amount of MMP-9

mRNA and protein begins to decrease. <>Moreover, MMP-9 is localized in inflammatory cells identified as polymorphonuclear leucocytes and macrophages. The MMP-2 activity is concurrent with the regeneration of new myofibers probably due to degradation of type IV collagen of the basement membrane during myoblast proliferation, migration and fusion. Conversely, MMP-9 might be associated with not only ECM degradation during inflammation, but also activating satellite cells during the initiation of muscle regeneration. Studies also indicated that MMP-1 can effectively reduce muscle scarring and that its activity is related to the ability of the enzyme to digest collagen, thereby facilitating remodeling and regeneration of the injured muscle. In a mouse model with muscle injury, C2C12 cells were transplanted with exogenous MMP-1 at the site of injury, resulting in the MMP-1 treated limbs contained greater regenerating myofibers and less fibrous scar tissue, which indicates that MMP-1 could enhance muscle regeneration by increasing the number of myofibers and decreasing the amount of fibrous tissue"[54.2]

[2] "<>The aim of this study was to assess the effects of resistance training on ladders (RTL) on MMP(-2) expression and blood lactate concentration [La-]. 30 male (3 months of age), albino rats were divided into 3 groups: sedentary control (SC, n=10), low resistance exercise training (Low-IntRT, n=10) and high-intensive exercise training (High-IntRT, n=10).
<>Animals of High-IntRT were submitted to a progressively increasing overload in relation to body weight until exhaustion, while the Low-IntRT group performed the same exercise regimen with no external load. The program had a frequency of 3 times per week over 8 weeks. MMP(-2) expression of tibialis anterior muscle and [La-] were measured.
<>While there was a significant increase of MMP(-2) (pro-form) in both groups, only High-IntRT significantly increased MMP(-2) in active-form ($p<0.05$). Both trained groups exhibited an increase in [La-] when compared to controls, however, the increase in [La-] was significantly higher in the High-IntRT compared to Low-IntRT ($p<0.05$). Strong correlation was found between MMP(-2) (active form) and [La-] in High-IntRT ($r=0.91$). RTL in using low and high-intensity exercise can serve as a model to demonstrate different responses of MMP(-2) expression in an animal model. It appears active form expression of MMP(-2) is modulated by exercise intensity."[54.3]

Protein Kinase B (AKT) / The Akt Pathway

The Akt Pathway describes the activation of Protein Kinase B (AKT) by the prime mediator Insulin, and often, phytochemicals. Once Protein Kinase B is activated, mTORC1 activity is stimulated, contributing to enhanced cell growth (myogenesis, neurogenesis, cancer, cellular senescence). Although not a protein, but a process, the overactivation of the Akt Pathway is one of the leading biochemical contributors to accelerated cellular aging.

Even though the Akt Pathway promotes aging processes, it is neuroprotective through inhibition of GSK3B, making insulin therefore neuroprotective against the development of cognitive decline and Dementias, and offering an explanation as to why many common

neuroprotective phytochemicals activate the Akt Pathway, which puzzled me for many years.

The Akt Pathway is necessary for early life neurological development, and it is probable that inhibition of it in early life will noticeably hamper a child's intelligence during their most formidable years of learning.

[A] The Akt Pathway promotes cellular senescence.

"<>The phosphatidylinositol 3-kinase (PI3K)/AKT and RAS oncogenic signalling modules are frequently mutated in sporadic human cancer. Although each of these pathways has been shown to play critical roles in driving tumour growth and proliferation, their activation in normal human cells can also promote cell senescence. Although the mechanisms mediating RAS-induced senescence have been well characterised, those controlling PI3K/AKT-induced senescence are poorly understood. <>Here we show that PI3K/AKT pathway activation in response to phosphatase and tensin homolog (PTEN) knockdown, mutant PI3K, catalytic, α polypeptide (PIK3CA) or activated AKT expression, promotes accumulation of p53 and p21, increases cell size and induces senescence-associated β-galactosidase activity. We demonstrate that AKT-induced senescence is p53-dependent and is characterised by mTORC1-dependent regulation of p53 translation and stabilisation of p53 protein following nucleolar localisation and inactivation of MDM2. The underlying mechanisms of RAS and AKT-induced senescence appear to be distinct, demonstrating that different mediators of senescence may be deregulated during transformation by specific oncogenes. <>Unlike RAS, AKT promotes rapid proliferative arrest in the absence of a hyperproliferative phase or DNA damage, indicating that inactivation of the senescence response is critical at the early stages of PI3K/AKT-driven tumourigenesis. Furthermore, our data imply that chronic activation of AKT signalling provides selective pressure for the loss of p53 function, consistent with observations that PTEN or PIK3CA mutations are significantly associated with p53 mutation in a number of human tumour types. <>Importantly, the demonstration that mTORC1 is an essential mediator of AKT-induced senescence raises the possibility that targeting mTORC1 in tumours with activated PI3K/AKT signalling may exert unexpected detrimental effects due to inactivation of a senescence brake on potential cancer-initiating cells."[54.4]

[B] Protein Kinase B (Akt) is neuroprotective through inhibiting GSK3B through phosphorylating it. GSK3B promotes apoptosis due to stimulating caspase production. Akt is necessary for exercise-induced neurogenesis[1] and by extension Insulin exerts its cellular protective effects through the Akt Pathway[2].

[1] "<>Background: Physical exercise has been shown to increase adult neurogenesis in the dentate gyrus and enhances synaptic plasticity. The antiapoptotic kinase, Akt has also been shown to be phosphorylated following voluntary exercise; however, it remains unknown whether the PI3K-Akt signaling pathway is involved in exercise-induced neurogenesis and the associated facilitation of synaptic plasticity in the dentate gyrus.

<>Methodology/principal findings: To gain insight into the potential role of this signaling pathway in exercise-induced neurogenesis and LTP in the dentate gyrus rats were infused with the PI3K inhibitor, LY294002 or vehicle control solution (icv) via osmotic minipumps and exercised in a running wheel for 10 days. Newborn cells in the dentate gyrus were date-labelled with BrdU on the last 3 days of exercise. Then, they were either returned to the home cage for 2 weeks to assess exercise-induced LTP and neurogenesis in the dentate gyrus, or were killed on the last day of exercise to assess proliferation and activation of the PI3K-Akt cascade using western blotting.
<>Conclusions/significance: Exercise increases cell proliferation and promotes survival of adult-born neurons in the dentate gyrus. Immediately after exercise, we found that Akt and three downstream targets, BAD, GSK3beta and FOXO1 were activated. LY294002 blocked exercise-induced phosphorylation of Akt and downstream target proteins. This had no effect on exercise-induced cell proliferation, but it abolished most of the beneficial effect of exercise on the survival of newly generated dentate gyrus neurons and prevented exercise-induced increase in dentate gyrus LTP.
<>These results suggest that activation of the PI3 kinase-Akt signaling pathway plays a significant role via an antiapoptotic function in promoting survival of newly formed granule cells generated during exercise and the associated increase in synaptic plasticity in the dentate gyrus."[54.5]

[2] "<>Glycogen synthase kinase-3 (GSK3) is implicated in the regulation of several physiological processes, including the control of glycogen and protein synthesis by insulin, modulation of the transcription factors AP-1 and CREB, the specification of cell fate in Drosophila and dorsoventral patterning in Xenopus embryos. GSK3 is inhibited by serine phosphorylation in response to insulin or growth factors and in vitro by either MAP kinase-activated protein (MAPKAP) kinase-1 (also known as p90rsk) or p70 ribosomal S6 kinase (p70S6k).
<>Here we show, however, that agents which prevent the activation of both MAPKAP kinase-1 and p70S6k by insulin in vivo do not block the phosphorylation and inhibition of GSK3. Another insulin-stimulated protein kinase inactivates GSK3 under these conditions, and we demonstrate that it is the product of the proto-oncogene protein kinase B (PKB, also known as Akt/RAC). Like the inhibition of GSK3 (refs 10, 14), the activation of PKB is prevented by inhibitors of phosphatidylinositol (PI) 3-kinase."[54.6]

[See: Anti-Aging, Lifespan Extension, & Longevity Diets]

[See: Anti-Inflammation Cycle Supplementation: Lithium]

Hypoxia-inducible Factor-1a (HIF-1)

HIF-1a is a very interesting energy sensing protein similar to AMPK that is activated (stabilized) within cells following tissue exposure to energy stress, specifically oxygen deprivation (hypoxia). It stimulates angiogenesis, and I believe associated with or directly promotes stem cell proliferation, to facilitate cellular adaptation towards low oxygen

conditions, including Endurance Training, and Occlusion Training. HIF-1a also appears to stimulate autophagy.

[A] "<>The cardiovascular system ensures the delivery of oxygen and nutrients to all cells, tissues, and organs. Under extended exposure to reduced oxygen levels, cells are able to survive through the transcriptional activation of a series of genes that participate in angiogenesis, glucose metabolism, and cell proliferation. The oxygen-sensitive transcriptional activator HIF-1 (hypoxia-inducible factor-1) is a key transcriptional mediator of the response to hypoxic conditions. The HIF-1 pathway was found to be a master regulator of angiogenesis. Whether the process is physiological or pathological, HIF-1 seems to participate in vasculature formation by synergistic correlations with other proangiogenic factors such as VEGF (vascular endothelial growth factor), PlGF (placental growth factor), or angiopoietins. Considering the important contributions of HIF-1 in angiogenesis and vasculogenesis, it should be considered a promising target for treating ischaemic diseases or cancer. In this review, we discuss the roles of HIF-1 in both physiological/pathophysiological angiogenesis and potential strategies for clinical therapy."[54.7]

[B] Below we learn, coming from the researchers Malene E. Lindholm, & Helene Rundqvist, that the HIF-1a response to aerobic-endurance exercise appears to reach a plateau, possibly paralleling a decrease in exercise-induced skeletal muscle angiogenesis, and making it important (if angiogenesis is the goal of training) to cycle between high volume and low volume, occluded and not occluded workouts, or detrain every month or two. Furthermore, HIF-1a appears to be associated with a fast twitch phenotype, due to reducing oxidative metabolism, although this seems contradictory, HIF-1a does not remain elevated in skeletal muscle following exercise, therefore HIF-1a clearly serves the role of stimulating immediate adaptation following exercise or oxygen-glucose deprivation.

"<>Reduced oxygen levels in skeletal muscle during exercise are a consequence of increased oxygen consumption. The cellular response to hypoxia is conferred to a large extent by activation of the hypoxia-sensitive transcription factor hypoxia-inducible factor-1 (HIF-1). The target genes of HIF-1 increase oxygen transport through mechanisms such as erythropoietin-mediated erythropoiesis and vascular endothelial growth factor-induced angiogenesis and improve tissue function during low oxygen availability through increased expression of glucose transporters and glycolytic enzymes, which makes HIF-1 an interesting candidate as a mediator of skeletal muscle adaptation to endurance training. However, HIF-1 may also inhibit cellular oxygen consumption and mitochondrial oxidative metabolism, features discordant with the phenotype of a trained muscle. Skeletal muscle readily adjusts to altered functional demands. Adaptation of skeletal muscle to long-term aerobic training enables better aerobic performance at higher intensities through improved metabolic capacity and oxygen supply.
<>The components of acute exercise that act as triggers for adaptation are still largely unknown; however, an early hypothesis was that local hypoxia acts as a possible stimulus

for exercise adaptation. The hypoxia-sensitive subunit, HIF-1α, is stabilized in skeletal muscle in response to an acute bout of endurance exercise. However, long-term endurance exercise seems to attenuate the acute HIF-1α response. This attenuation is concurrent with an increase in expression of several negative regulators of the HIF system.

<>We propose that the HIF-1α response is blunted in response to long-term exercise training through induction of its negative regulators and that this inhibition enables the enhanced oxidative metabolism that is part of a local physiological response to exercise."

↓ continued

"<>Downregulation of HIF-1 activity with long-term aerobic training could be interpreted as part of the attenuation in the exercise response known to follow after a longer training period. Tissue-specific deletions are the best available experimental models to isolate the unique function of individual proteins in vivo, despite possible compensatory effects.

<>Interestingly, mice with a skeletal muscle-specific deletion of HIF-1α perform better in swimming and running endurance trials and show several of the features associated with a trained muscle, especially in relation to mitochondrial characteristics, such as enzyme activities of citrate synthase and 3-hydroxyacyl-CoA dehydrogenase (Mason et al. 2004, 2007). This implies that a loss of skeletal muscle HIF-1 may be beneficial for oxidative capacity and endurance performance. However, it should also be noted that these knockout mice display extensive muscle damage in response to downhill running.

<>The effect of the HIF-1α knockout on mitochondrial function was suggested to be due to activation of the pyruvate dehydrogenase complex (PDHc) through the reduced activity of the HIF-1-inducible inhibitor of PDHc, pyruvate dehydrogense kinase 1 (PDK-1). Hypoxia-inducible factor-1 regulates mitochondrial oxygen consumption in cells during hypoxia through increased expression of PDK-1 (Kim et al. 2006), which inhibits PDHc and provides an active repression of mitochondrial function to reduce the cellular oxygen consumption.

<>In the knockout mice, reduction of HIF-1α activity led to attenuated PDK-1 levels at rest and after an acute bout of exercise, which could explain the enhanced mitochondrial function and the reduced lactate accumulation seen after exercise (Mason et al. 2004, 2007). In humans, individuals suffering from the autosomal recessive disorder Chuvash polycythaemia carry a mutation in the Von Hippel–Lindau protein (VHL) gene, leading to a general stabilization of HIF-1. The elevated HIF-1 activity alters skeletal muscle metabolism and leads to reduced muscle pH and increased serum lactate accumulation in response to exercise, as well as a reduction in maximal exercise performance in these patients. Transcriptional analyses of skeletal muscle showed enhanced levels of the HIF-1 targets Phosphofructokinase and PDK-1, indicating high glycolytic activity (Formenti et al. 2010).

<>In the current literature, there is evidence that HIF-1 not only activates glycolytic pathways but that it also suppresses mitochondrial function and is responsible for a reduction in mitochondrial activity and oxygen consumption. Several studies indicate that HIF-1 actively decreases the levels of the mitochondrially encoded components of the oxidative phosphorylation pathway in skeletal muscle through interactions with myc-1

(Zhang et al. 2007; Gomes et al. 2013). It has also been suggested that increased fatty acid oxidation may be compensating for decreased flow through the glycolytic pathway in supplying the citric acid cycle with acetyl CoA (Mason et al. 2004). A third explanation may be that HIF-1 actively inhibits oxidative capacity through constraining the expression and/or function of the important coactivator of oxidative capacity, peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α; LaGory et al. 2015)."[54.8]

[C] HIF-1a promotes autophagy through Beclin1 expression.

"<>Hypoxic preconditioning (HPC) exerts a protective effect against hypoxic/ischemic brain injury, and one mechanism explaining this effect may involve the upregulation of hypoxia-inducible factor-1 (HIF-1). Autophagy, an endogenous protective mechanism against hypoxic/ischemic injury, is correlated with the activation of the HIF-1α/Beclin1 signaling pathway. Based on previous studies, we hypothesize that the protective role of HPC may involve autophagy occurring via activation of the HIF-1α/Beclin1 signaling pathway.
<>To test this hypothesis, we evaluated the effects of HPC on oxygen-glucose deprivation/reperfusion (OGD/R)-induced apoptosis and autophagy in SH-SY5Y cells. HPC significantly attenuated OGD/R-induced apoptosis, and this effect was suppressed by the autophagy inhibitor 3-methyladenine and mimicked by the autophagy agonist rapamycin. In control SH-SY5Y cells, HPC upregulated the expression of HIF-1α and downstream molecules such as BNIP3 and Beclin1. <>Additionally, HPC increased the LC3-II/LC3-I ratio and decreased p62 levels. The increase in the LC3-II/LC3-I ratio was inhibited by the HIF-1α inhibitor YC-1 or by Beclin1-short hairpin RNA (shRNA). In OGD/R-treated SH-SY5Y cells, HPC also upregulated the expression levels of HIF-1α, BNIP3, and Beclin1, as well as the LC3-II/LC3-I ratio.
<>Furthermore, YC-1 or Beclin1-shRNA attenuated the HPC-mediated cell viability in OGD/R-treated cells. Taken together, our results demonstrate that HPC protects SH-SY5Y cells against OGD/R via HIF-1α/Beclin1-regulated autophagy."[54.9]

Signal Transducer and Activator of Transcription 3 (STAT3)

STAT3 is an inflammatory protein activated by IL-6 that is associated with wound healing, aging, & autoimmunity by way of inflammatory cytokine signaling. Moderate activity of STAT3 is important for wound regeneration (myogenesis) but high activity will cause muscle atrophy and muscle fibrosis.

[A] STAT3 activity increases with age.

"<>Activation of the transcription factor signal transducers and activators of transcription (STAT) 3 is common to many inflammatory cytokines and growth factors, with recent evidence of involvement in skeletal muscle regeneration. The purpose of this study was to determine whether STAT3 signaling activation is regulated differentially, at rest and

following intense resistance exercise, in aged human skeletal muscle. Skeletal muscle biopsies were harvested from healthy younger (n = 11, 20.4 +/- 0.8 years) and older men (n = 10, 67.4 +/- 1.3 years) under resting conditions and 2 h after the completion of resistance exercise. No differences were evident at rest, whereas the phosphorylation of STAT3 was significantly increased in old (23-fold) compared to young (5-fold) subjects after exercise.
<>This correlated with significantly higher induction of the STAT3 target genes including; interleukin-6 (IL-6), JUNB, c-MYC, and suppressor of cytokine signaling (SOCS) 3 mRNA in older subjects following exercise. Despite increased SOCS3 mRNA, cellular protein abundance was suppressed. SOCS3 protein is an important negative regulator of STAT3 activation and cytokine signaling.
<>Thus, in aged human muscle, elevated responsiveness of the STAT3 signaling pathway and suppressed SOCS3 protein are evident following resistance exercise. These data suggest that enhanced STAT3 signaling responsiveness to proinflammatory factors may impact on mechanisms of muscle repair and regeneration."[55]

[B] STAT3 is important for myogenic differentiation.

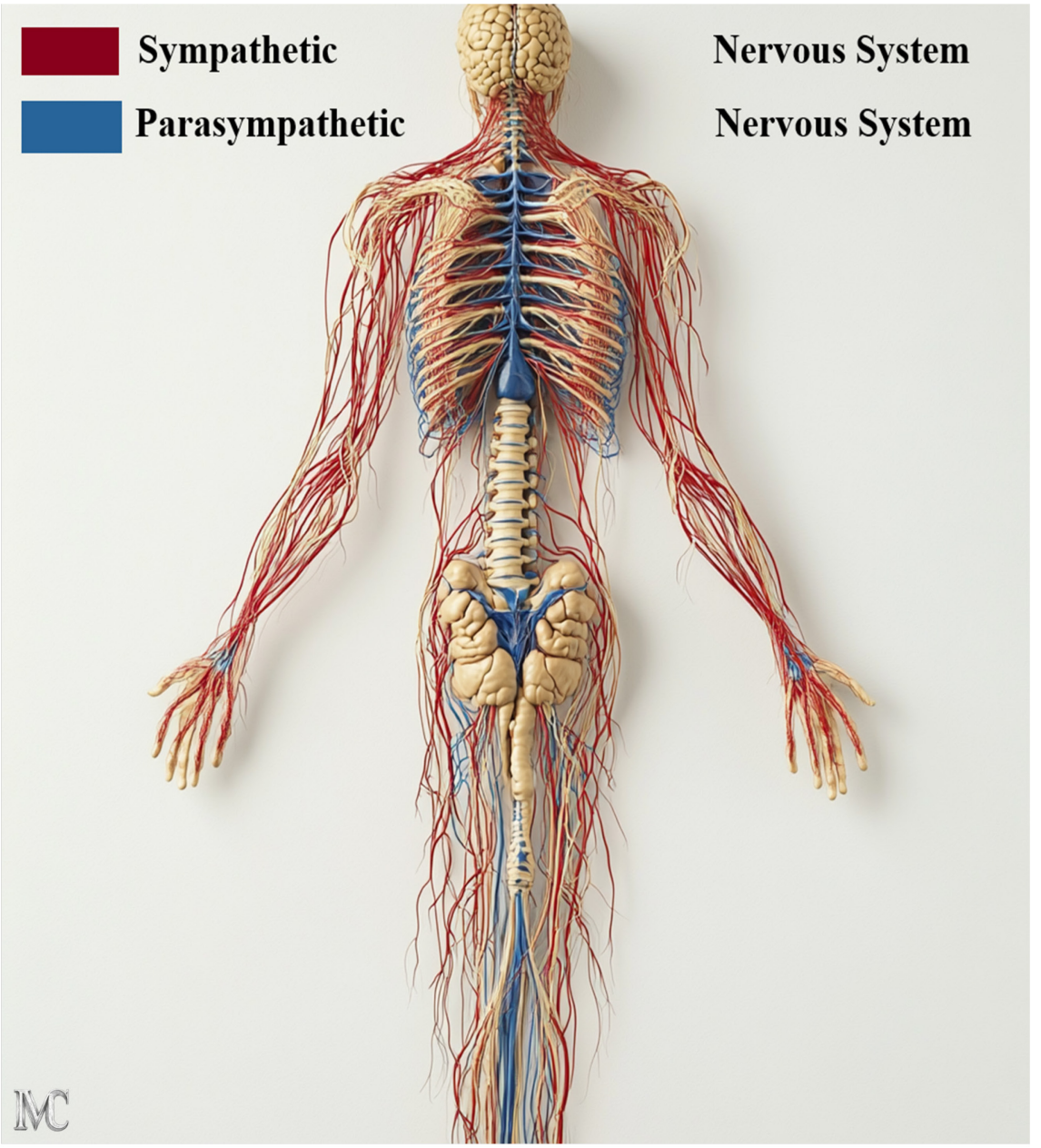
"<>Skeletal muscle satellite cell-derived myoblasts are mainly responsible for postnatal muscle growth and injury-induced regeneration. However, the cellular signaling pathways that control proliferation and differentiation of myoblasts remain poorly defined. Recently, we found that JAK1/STAT1/STAT3 not only participate in myoblast proliferation but also actively prevent them from premature differentiation.
<>Unexpectedly, we found that a related pathway consisting of JAK2, STAT2, and STAT3 is required for early myogenic differentiation. Interference of this pathway by either a small molecule inhibitor or small interfering RNA inhibits myogenic differentiation. Consistently, all three molecules are activated upon differentiation.
<>The pro-differentiation effect of JAK2/STAT2/STAT3 is partially mediated by MyoD and MEF2. Interestingly, the expression of the IGF2 gene and the HGF gene is also regulated by JAK2/STAT2/STAT3, suggesting that this pathway could also promote differentiation by regulating signaling molecules known to be involved in myogenic differentiation. In summary, our current study reveals a novel role for the JAK2/STAT2/STAT3 pathway in myogenic differentiation."[56]

The Nervous System

The Nervous System, especially the spine and all of its innervating nerves, is to be considered the secondary director, displacer, and actuator of locomotive potential.
We do not often think of the health of our nerves until damage is done, through exercise, or environmental toxin exposure. The best way to strengthen and regenerate nerves is by increasing Nerve Growth Factor, its name is apropos to its effects. The only proven way to enhance NGF systemically, and not just in the brain, is to experiment with the supplementation of large dosages of medicinal mushrooms,

See: Anti-Inflammation Cycle Supplementation: Lion's Mane Mushroom Powder.

For information on the "Second Brain", the *Enteric Nervous System*, that of which lines the intestines, See: Probiotics, Fibers, & Short Chain Fatty Acids.



An introduction to the Nervous System from the Institute for Quality and Efficiency in Health Care, Cologne, Germany:

“<>The nervous system is made up of all the nerve cells in your body. It is through the nervous system that we communicate with the outside world and, at the same time, many mechanisms inside our body are controlled. The nervous system takes in information through our senses, processes the information and triggers reactions, such as making your muscles move or causing you to feel pain. For example, if you touch a hot plate, you reflexively pull back your hand and your nerves simultaneously send pain signals to your brain. Metabolic processes are also controlled by the nervous system.
<>There are many billions of nerve cells, also called neurons, in the nervous system. The brain alone has about 100 billion neurons in it. Each neuron has a cell body and various extensions. The shorter extensions (called dendrites) act like antennae: they receive signals from, for example, other neurons and pass them on to the cell body. The signals are then passed on via a long extension (the axon), which can be up to a meter long.
<>The nervous system has two parts, called the central nervous system and the peripheral nervous system due to their location in the body. The central nervous system (CNS) includes the nerves in the brain and spinal cord. It is safely contained within the skull and vertebral canal of the spine. All of the other nerves in the body are part of the peripheral nervous system (PNS).
<>Regardless of where they are in the body, a distinction can also be made between voluntary and involuntary nervous system. The voluntary nervous system (somatic nervous system) controls all the things that we are aware of and can consciously influence, such as moving our arms, legs, and other parts of the body.
<>The involuntary nervous system (vegetative or autonomic nervous system) regulates the processes in the body that we cannot consciously influence. It is constantly active, regulating things such as breathing, heartbeat and metabolic processes. It does this by receiving signals from the brain and passing them on to the body. It can also send signals in the other direction – from the body to the brain – providing your brain with information about how full your bladder is or how quickly your heart is beating, for example. The involuntary nervous system can react quickly to changes, altering processes in the body to adapt. For instance, if your body gets too hot, your involuntary nervous system increases the blood circulation to your skin and makes you sweat more to cool your body down again.
<>Both the central and peripheral nervous systems have voluntary and involuntary parts. However, whereas these two parts are closely linked in the central nervous system, they are usually separate in other areas of the body.
<>The involuntary nervous system is made up of three parts:

1. The sympathetic nervous system.
2. The parasympathetic nervous system.
3. The enteric (gastrointestinal) nervous system.

<>The sympathetic and parasympathetic nervous systems usually do opposite things in the body. The sympathetic nervous system prepares your body for physical and mental

activity. It makes your heartbeat faster and stronger, opens your airways so you can breathe more easily, and inhibits digestion.
<>The parasympathetic nervous system is responsible for bodily functions when we are at rest: it stimulates digestion, activates various metabolic processes, and helps us to relax. But the sympathetic and parasympathetic nervous systems do not always work in opposite directions; they sometimes complement each other too."[57.A]

[A] Our Nervous System appears to have adapted through evolutionary processes to increase sociality and dampen stress signaling in our brains i.e. through reduced HPA axis activity, explained as the Polyvagal Theory in [1]-[2].

[1] "The polyvagal theory (PT), offered by Porges (2021), proposes that the autonomic nervous system (ANS) was repurposed in mammals, via a "second vagal nerve", to suppress defensive strategies and support the expression of sociality".[57.B]

[2] "<>Investigation of the phylogeny of the vertebrate autonomic nervous system provides an answer to the vagal paradox. Research in comparative neuroanatomy and neurophysiology has identified two branches of the vagus, with each branch supporting different adaptive functions and behavioral strategies. The vagal output to the heart from one branch is manifested in respiratory sinus arrhythmia, and the output from the other branch is manifested in bradycardia and possibly the slower rhythms in heart rate variability. Although the slower rhythms have been assumed to have a sympathetic influence, they are blocked by atropine.
<>The polyvagal theory articulates how each of three phylogenetic stages in the development of the vertebrate autonomic nervous system is associated with a distinct autonomic subsystem that is retained and expressed in mammals. These autonomic subsystems are phylogenetically ordered and behaviorally linked to social communication (eg, facial expression, vocalization, listening), mobilization (eg, fight–flight behaviors), and immobilization (eg, feigning death, vasovagal syncope, and behavioral shutdown).
<>The social communication system (ie, social engagement system; see below) involves the myelinated vagus, which serves to foster calm behavioral states by inhibiting sympathetic influences to the heart and dampening the hypothalamic-pituitary-adrenal (HPA) axis. The mobilization system is dependent on the functioning of the sympathetic nervous system.
<>The most phylogenetically primitive component, the immobilization system, is dependent on the unmyelinated vagus, which is shared with most vertebrates. With increased neural complexity resulting from phylogenetic development, the organism's behavioral and affective repertoire is enriched. The three circuits can be conceptualized as dynamic, providing adaptive responses to safe, dangerous, and life-threatening events and contexts."
"<>Functionally, when the environment is perceived as safe, two important features are expressed. First, [the] bodily state is regulated in an efficient manner to promote growth

and restoration (eg, visceral homeostasis). This is done through an increase in the influence of mammalian myelinated vagal motor pathways on the cardiac pacemaker that slows the heart, inhibits the fight–flight mechanisms of the sympathetic nervous system, dampens the stress response system of the HPA axis (eg, cortisol), and reduces inflammation by modulating immune reactions (eg, cytokines). <>Second, through the process of evolution, the brainstem nuclei that regulate the myelinated vagus became integrated with the nuclei that regulate the muscles of the face and head. This link results in the bidirectional coupling between spontaneous social engagement behaviors and bodily states. Specifically, an integrated social engagement system emerged in mammals when the neural regulation of visceral states that promote growth and restoration (via the myelinated vagus) was linked neuroanatomically and neurophysiologically with the neural regulation of the muscles controlling eye gaze, facial expression, listening, and prosody"

"<>The human nervous system, similar to that of other mammals, evolved not solely to survive in safe environments but also to promote survival in dangerous and life-threatening contexts. To accomplish this adaptive flexibility, the human nervous system retained two more primitive neural circuits to regulate defensive strategies (ie, fight–flight and death-feigning behaviors). It is important to note that social behavior, social communication, and visceral homeostasis are incompatible with the neurophysiological states and behaviors promoted by the two neural circuits that support defense strategies. Thus, via evolution, the human nervous system retains three neural circuits, which are in a phylogenetically organized hierarchy. In this hierarchy of adaptive responses, the newest circuit is used first; if that circuit fails to provide safety, the older circuits are recruited sequentially."[57.C]

Heart Rate Variability (HRV)

Heart Rate Variability describes the time intervals between heart beats, not to be confused with heart rate, which only describes the number of heart beats per minute. Activation of the Sympathetic Nervous System results in increased heart rate, and decreased HRV, whereas activation of the Parasympathetic Nervous System results in decreased heart rate, and increased HRV.

Heart rate variability can be considered the *cognitive flexibility of the heart* in my opinion, as higher HRV is associated with positive behavioral indices as detailed in the following study by Baljinder K. Sahdra, Joseph Ciarrochi, & Philip D. Parker:

"<>Human beings are fundamentally social. Are there biological factors that predispose us to affiliate with groups? One likely candidate is the cardiac vagal tone or the autonomic influence on heart rate. A healthy heart has a fluctuating rhythm. The normal variability in heart rate occurs, in part, from the synergistic actions of the sympathetic and parasympathetic branches of the autonomic nervous system (ANS), which allow the cardiovascular system to adapt to varying internal biological conditions as well as external situations. Fluctuations in heart rate that occur at the high frequency (0.15 to 0.4 Hz) range are considered to clearly represent the chronotropic effect of the

parasympathetic nervous system on the heart via the vagus (10th cranial) nerve, and are linked to Respiratory Sinus Arrhythmia (RSA), the increase and decrease in heart rate with inhalation and exhalation, respectively. High-frequency heart rate variability (HF-HRV), as measured under resting conditions, represents a relatively stable autonomic disposition.

<>There is a growing body of evidence linking HF-HRV with individual differences in regulation of emotions and cognitive functions: High HF-HRV is linked to positive emotions and interpersonal connectedness, stability of positive affect in daily life, better emotional responding and affect regulation, greater cognitive performance, better attention regulation, better impulse control, and better self-regulation. To the extent that HF-HRV can be interpreted as a trait of ANS response to the environment, it might also be linked to social adaptability in a situation where people have a chance to affiliate with new groups.

<>This makes sense theoretically because the "vagal brake" on heart rate allows efficient use of glucose to meet the metabolic costs of social information processing, and flexible redirecting of energy from the periphery to the brain to better attend to situational cues. Based on these theoretical perspectives and empirical studies showing positive relationship between cardiac vagal tone and various aspects of socio-cognitive functioning, one can expect a link between HF-HRV and individual differences in the ease with which people can affiliate with novel groups.

<>People are generally motivated to identify themselves with social groups, often derive their self-regard at least partly from their group memberships, and tend to favour the groups to which they belong (ingroups) compared to the groups to which they do not belong (outgroups). A mere categorization of the self as a member of a totally new group about which one knows very little and has not even met any other member of that group, can be enough to elicit ingroup favouritism. In a typical minimal group paradigm, participants are randomly assigned to one of two groups based on an arbitrary criterion (e.g., colour of shirts, preferences for art work) and later asked to evaluate or allocate money to members of the two groups. People tend to favour their own newly formed group at the expense of the other group. It is noteworthy that ingroup favouritism is not the same as outgroup derogation, which can involve holding negative attitudes towards the outgroup or actively harming outgroup members. The minimal group paradigm has been well-studied for over 40 years and the phenomenon of ingroup favouritism in minimal groups is among the most robust findings in social psychology."

"<>In a socially threatening or unsafe situation, the influence of the vagus nerve on the body is expected to be minimized or shut down to redirect metabolic resources for a flight/fight response; whereas in a relatively safe social situation, the influence of the vagus is expected to be increased or maintained to promote calm behavioural states, self-regulation and prosocial/affiliative responses. Social psychological studies have found that cardiac vagal tone is negatively associated with attachment anxiety and perceived lack of security in close relationships, and marital conflict; and positively associated with perceived social support, positive emotions and feelings of connectedness during social interactions, having more supporting friends, and coping with sadness with higher social engagement."[57.D]

[A] Parasympathetic Nervous System power (High frequency heart rate fluctuations), which is dependent on Vagus Nerve activity, decreases following resistance training, returns to baseline after 24 hours of recovery, and increases above baseline following 48 hours of recovery. Higher intensity forms of exercise, through an evolutionary viewpoint, occurred primarily during an escape from predators, thus explaining why HRV decreases following HIT Training[A2], in that as a survival mechanism, a reduction in Vagus Nerve activity following stress is necessary to prepare our bodies for another immediate flight-or-fight response by facilitating the Sympathetic Nervous System, at the cost of decreased behavioral manifestations, such as sociality. This explains, at the very least partially, aside from increased bDNF expression, the potentially deleterious but subtle changes to mood that accompany higher intensity forms of exercise.

"<>Heart rate variability (HRV) and parasympathetic power are closely related to the well-being and health status in humans. The main goal of the study was to determine whether these measures can reflect recovery status after weight training. After a 10-day detraining period, 7 weightlifters were challenged with a 2-hour weight training which elicited approximately fourfold increases in circulating muscle creatine kinase level and protracted pain feeling ($p < 0.05$). Weightlifting performance was then evaluated 3, 24, 48, and 72 hours after training to determine the degree of recovery from fatigue. Heart rate variability, circulating dehydroepiandrostendione sulfate (DHEA-S), and muscle damage markers were measured before each performance test. An electrocardiogram was recorded for 5 minutes continuously at rest in seated positions.
<>After training, weightlifting performance of the subjects decreased below baseline in paralleled with suppressed parasympathetic power (high-frequency [HF] HRV), whereas sympathetic power (normalized low-frequency HRV) was slightly elevated at 3 hours of recovery ($p < 0.05$). Both weightlifting performances and parasympathetic power returned to baseline values in 24 hours and further increased above baseline during 48-72 hours of recovery in a similar fashion ($p < 0.05$). Circulating DHEA-S level dropped at 24 hours ($p < 0.05$) and returned to normal values by 48 hours. Muscle pain increased at 3 hours after training and remained higher than baseline values for the 72-hour recovery period ($p < 0.05$).
<>Our data suggest that parasympathetic power, indicated by HF HRV, is able to reflect the recovery status of weightlifters after training."[57.E]

[A2] Endurance Training, as opposed to HIT Training, strengthens the Parasympathetic Nervous System.

"<>It is well established that endurance exercise has positive effects on cardiac autonomic function (CAF). However, there is still a dearth of information about the effects of regular high-intensity interval training combined with different types of exercises (HIITCE) on CAF.
<>Objective: The aim of this study is to compare CAF at rest, its reactivity, and reactivation following maximal exercise testing in HIITCE and endurance athletes.

<>Methods: An observational study was conducted with 34 male athletes of HIITCE (i.e., CrossFit) [HG: n = 18; 30.6 ± 4.8 years] and endurance athletes (i.e., triathlon) [TG.: n = 16; 32.8 ± 3.6 years]. We analyzed 5 min of frequency-domain indices (TP, LF, HF, LFn, HFn, and LF/HF ratio) of heart rate variability (HRV) in both supine and orthostatic positions and its reactivity after the active orthostatic test. Post-exercise heart rate recovery (HRR) was assessed at 60, 180, and 300 s. Statistical analysis employed a non-parametric test with a p-value set at 5%.
<>Results: The HG showed reduced HFn and increased LFn modulations at rest (supine). Overall cardiac autonomic modulation (TP) at supine and all indices of HRV at the orthostatic position were similar between groups. Following the orthostatic test, the HG showed low reactivity for all HRV indices compared to TG. After the exercise, HRR does not show a difference between groups at 60 s. However, at 180 and 300 s, an impairment of HRR was observed in HG than in TG.
<>Conclusion: At rest (supine), the HG showed reduced parasympathetic and increased sympathetic modulation, low reactivity after postural change, and impaired HRR compared to TG." [57.F]

[See: Probiotics, Fibers, & Short Chain Fatty Acids: The Enteric Nervous System]

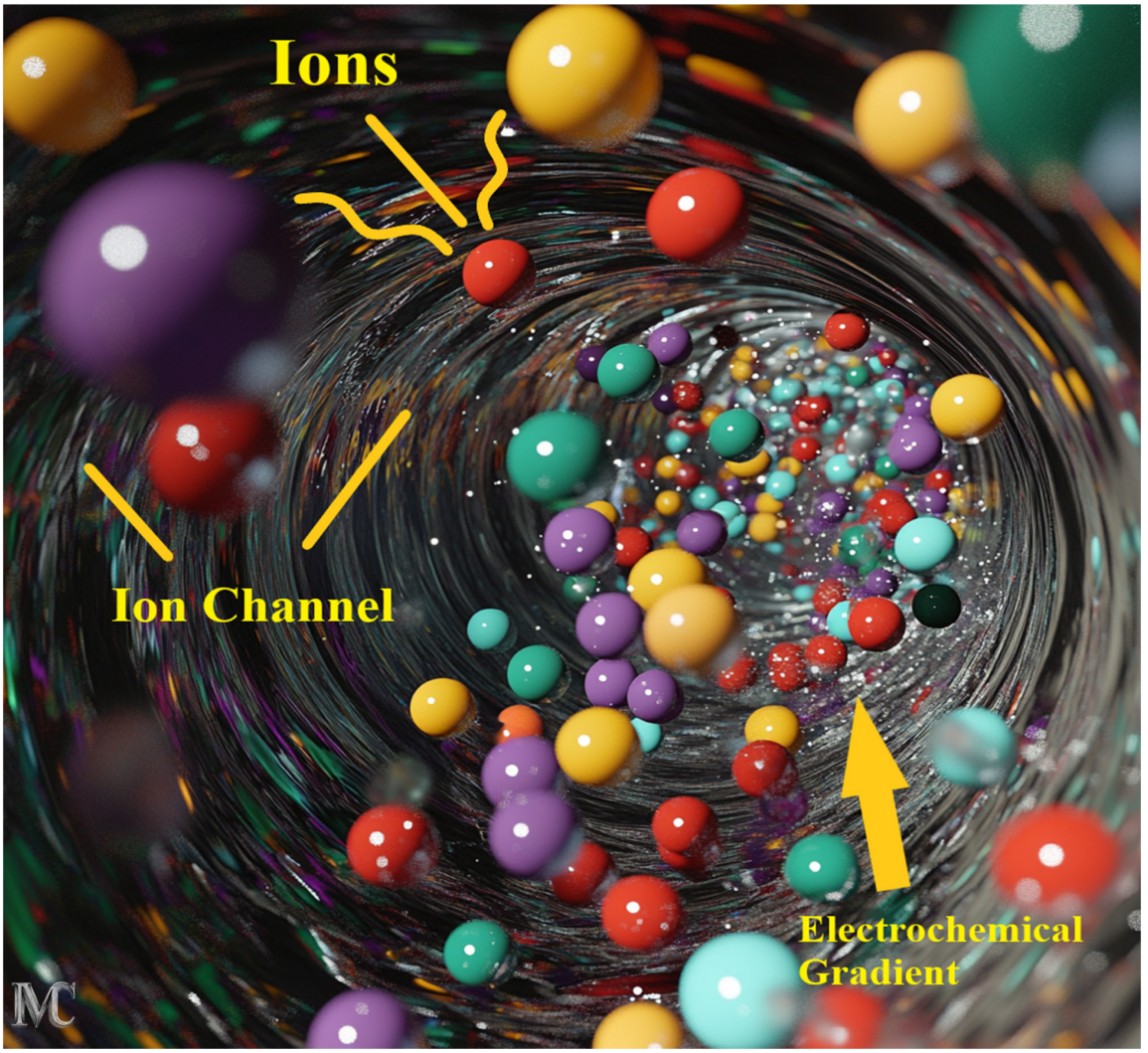
Ion Channels

Ions are carriers of electrical charge; they are essential for the facilitation of all forms of life due to being prerequisites for nerve conduction, cellular signaling, and even the metabolism and growth of microorganisms, among many other complex life processes. Most Ions come from Elements that have undergone chemical reactions, while others come from radiation, biological processes such as Cellular Respiration, or Photosynthesis.

Ion Channels are found in every cell, they facilitate the spread of Ions across cell membranes, whereas the Electrochemical Gradient is similar to a Battery and controls the flow of Ions within Ion Channels through voltage changes, which can either accelerate or decelerate Ion flow. The major Ions in the human body in relation to skeletal muscle and neurology are the Ca2+ (Calcium Ions) [A], K+ (Potassium Ions) [B], & Na+ (Sodium Ions) [C], they are necessary for both muscle contraction, myogenesis, and neurological activity, and they increase in activity in the body from Electrolyte consumption.

Electrolytes are essential nutrients that must be supplemented in athletes, especially ones who engage in competitive sports wherein maximized muscle performance is the primary focus.

Ion Channels do not only relate to the electrophysiological changes in our muscles, but they also associate with neurological dynamics, and quite possibly, the generation and facilitation of consciousness, such as in the ORCH-OR Theory, and my idea that ions drastically affect microtubule growth and decay, leading to the conclusion that electrolyte deprivation affects not only intelligence, but actual consciousness.



Ions & The Orchestrated Objective Reduction Theory (ORCH-OR)

A new theory on Quantum Consciousness, ORCH-OR, has been proposed by Roger Penrose and Stuart Hameroff which posits the basis for consciousness fundamentally coming from the interactions and activity of microtubules, which exist within every cell. Microtubules oscillate and assemble and disassemble rapidly, thus making them great candidates for the explanation for the development and facilitation of consciousness. I believe this theory can be merged directly with ions, as a small concentration of ions flow through microtubules, and this may explain a small or large part of microtubule dynamics. Strangely, these Microtubules may be directly associated with String Theory, as when the theorized Strings in our Universe oscillated, particles are were made, and when Microtubules oscillate and entangle, consciousness is facilitated.

Regarding Quantum Consciousness:

Quantum Coherence is term used to describe superposition (the existence of a system in multiple states simultaneously), entanglement (quantum system connection), and interference (the generation of wave-like behavior). Consciousness in this view is described as:

1. Quantum Coherence: The efficient transfer of information and the entanglement of microtubule networks.

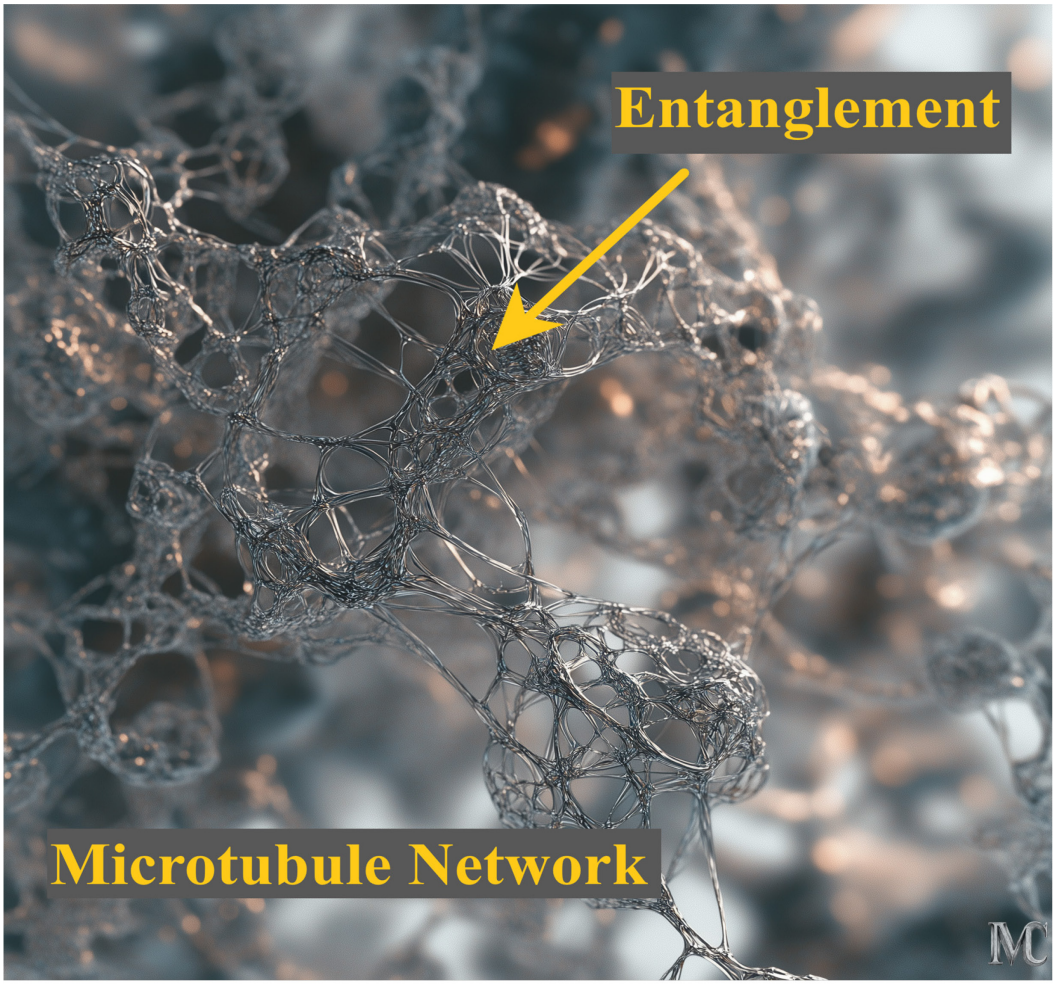
2. Superposition: Consciousness exists in multiple states which aligns with Freud's view of cathected and uncathected neurons, the conscious neurons, and the unconscious neurons i.e. engram neurons and silent-engrams neurons.

3. Interference: Environmental interactions such as Ion concentration changes disrupt Quantum Coherence, leading to memory formation and the generation of behaviors. This is Quantum Decoherence and is caused by entropy, which rises most prominently in the brain due to sensory sensations—distractions—the exigencies of existence (touch, sight, scent, hearing, pain).

I believe it is logical to suggest—and I am certain many other scientists have posited this—that the random movement of ions within microtubules cause Quantum Fluctuations, thus leading to changes and adaptations to consciousness, and this is what many consider free will, or a more accurate explanation in my view is *the comprehension of chaos (errors) within ordered systems* (retrospective memory processing to inform a finite sum of possible future decisions: Simplified: Forethought). Forethought in this view would be a form of cognitive time travel, which is an argument strengthened by the Transactional Interpretation where it is suggested that waves travel forward and backward in time, this forward and backward travel of waves would therefore be the universal progenitor of the Error-related Negativity mammals possess, which would have evolved (mutated) thereafter from Quantum Decoherence, that being microtubule disassembly. It is understood that higher forms of consciousness are dependent on Error processing i.e. the backward flow of waves (information), but this fact is not well known nor understood, and it leads me to the quantum mechanical idea that the nature of time is non-linear and bidirectional, as evidenced by Stuart Hameroff astute quantum mechanical clarification of the Free Will problem through ORCH-OR:

"<>Conscious "free will" is problematic because (1) brain mechanisms causing consciousness are unknown, (2) measurable brain activity correlating with conscious perception apparently occurs too late for real-time conscious response, consciousness thus being considered "epiphenomenal illusion," and (3) determinism, i.e., our actions and the world around us seem algorithmic and inevitable. The Penrose–Hameroff theory of "orchestrated objective reduction (Orch OR)" identifies discrete conscious moments with quantum computations in microtubules inside brain neurons, e.g., 40/s in concert with gamma synchrony EEG. Microtubules organize neuronal interiors and regulate synapses.

<>In Orch OR, microtubule quantum computations occur in integration phases in dendrites and cell bodies of integrate-and-fire brain neurons connected and synchronized by gap junctions, allowing entanglement of microtubules among many neurons. Quantum computations in entangled microtubules terminate by Penrose “objective reduction (OR),” a proposal for quantum state reduction and conscious moments linked to fundamental spacetime geometry. Each OR reduction selects microtubule states which can trigger axonal firings, and control behavior. The quantum computations are “orchestrated” by synaptic inputs and memory (thus “Orch OR”).
<>If correct, Orch OR can account for conscious causal agency, resolving problem 1. Regarding problem 2, Orch OR can cause temporal non-locality, sending quantum information backward in classical time, enabling conscious control of behavior. Three lines of evidence for brain backward time effects are presented. Regarding problem 3, Penrose OR (and Orch OR) invokes non-computable influences from information embedded in spacetime geometry, potentially avoiding algorithmic determinism.
<>In summary, Orch OR can account for real-time conscious causal agency, avoiding the need for consciousness to be seen as epiphenomenal illusion. Orch OR can rescue conscious free will.”[57.0]



[See: Dietary Fatty Acids: [E] Linoleic acid and Microtubules]

[A] Calcium ions are necessary for myoblast fusion. This means that Calcium is one of the most important Myogenic elements and supplements.

"<>The process of myoblast fusion during skeletal myogenesis is calcium regulated. Suppression of fusion is obtained by lowering medium [Ca2+] and re-initiated by raising medium [Ca2+]. Previously, we showed that such changes in medium [Ca2+] produced concomitant changes in myoblast [Ca2+] and that a critical cellular concentration of calcium must be present in myoblasts for fusion to occur. In this study, we report on further investigations on the relationship between myoblast [Ca2+] and fusion and also present data which suggest that an outer cell surface pool of calcium is involved in the fusion process.
<>Cellular [Ca2+] must reach greater than 0.8 pmoles/cell and the medium [Ca2+] must be greater than 0.2-0.4 mM for myoblast fusion to occur. These conditions do not have a trigger effect on the entire myoblast population; instead, myoblast fusion was a dose-dependent linear response. If medium [Ca2+] was not maintained at 0.9 mM then cellular [Ca2+] decreased below a critical 0.8 pmoles/cell nucleus and fusion ceased. The cell surface pool of calcium was detected with the calcium antagonist lanthanum. A defined culture medium with 0.9 mM Ca2+ was used to maintain cell viability, and to prevent precipitation of medium components and changes in medium pH with La3+ (0.1 mM). La3+ did not enter the myoblasts as detected by electron microscopy, did not inhibit Ca2+ movement into the cells and the cellular [Ca2+] was sufficient to promote myoblast fusion. Under these conditions, myoblast fusion was inhibited.
<>Morphologically, the fusion-suppressed myoblasts resembled those suppressed by lowered medium [Ca2+]. After removal of the fusion-block by washing, the myotubes that formed were equivalent to those present in unaltered cultures. These results suggest that a La3+ displaceable Ca2+ pool exists at the surface of myoblasts which is involved in myoblast fusion.
<>Thus, it appears that myoblast fusion is dependent on the continuous presence of cell surface calcium and an adequate intracellular Ca2+. An influx of calcium alone is not sufficient to promote myotube formation."[57.1]

[B] Potassium Ions promote Fast Twitch muscle (Extensor Digitorum Longus Muscle: Fast Twitch, Soleus Muscle: Slow Twitch) force output through increasing Calcium Ion saturation in muscle tissue.

"<>The extracellular K+ concentration ([K+]o) increases during physical exercise. We here studied whether moderately elevated [K+]o may increase force and power output during contractions at in vivo-like subtetanic frequencies and whether such potentiation was associated with increased cytosolic free Ca2+ concentration ([Ca2+]i) during contractions. Isolated whole soleus and extensor digitorum longus (EDL) rat muscles were incubated at different levels of [K+]o, and isometric and dynamic contractility were tested at various stimulation frequencies.

<>Furthermore, [Ca2+]i at rest and during contraction was measured along with isometric force in single mouse flexor digitorum brevis (FDB) fibers exposed to elevated [K+]o. Elevating [K+]o from 4 mM up to 8 mM (soleus) and 11 mM (EDL) increased isometric force at subtetanic frequencies, 2-15 Hz in soleus and up to 50 Hz in EDL, while inhibition was seen at tetanic frequency in both muscle types. Elevating [K+]o also increased peak power of dynamic subtetanic contractions, with potentiation being more pronounced in EDL than in soleus muscles. The force-potentiating effect of elevated [K+]o was transient in FDB single fibers, reaching peak after ~4 and 2.5 min in 9 and 11 mM [K+]o, respectively. At the time of peak potentiation, force and [Ca2+]i during 15-Hz contractions were significantly increased, whereas force was slightly decreased and [Ca2+]i unchanged during 50-Hz contractions.
<>Moderate elevation of [K+]o can transiently potentiate force and power during contractions at subtetanic frequencies, which can be explained by a higher [Ca2+]i during contractions."[57.2]

[B2] Potassium Channels promote myogenesis through enhanced mTOR expression, which makes Potassium an *anabolic electrolyte*. I believe Potassium Betahydroxybutyrate is an excellent choice for Potassium supplementation because it offers us two myogenic chemicals in one form.

"<>The activation of potassium channels and the ensuing hyperpolarization in skeletal myoblasts are essential for myogenic differentiation. However, the effects of K+ channel opening in myoblasts on skeletal muscle mass are unclear. Our previous study revealed that pharmacological activation of intermediate conductance Ca2+-activated K+ channels (IKCa channels) increases myotube formation. In this study, we investigated the effects of 5,6-dichloro-1-ethyl-1,3-dihydro-2H-benzimidazol-2-one (DCEBIO), a Ca2+-activated K+ channel opener, on the mass of skeletal muscle. Application of DCEBIO to C2C12 cells during myogenesis increased the diameter of C2C12 myotubes in a concentration-dependent manner. This DCEBIO-induced hypertrophy was abolished by gene silencing of IKCa channels. However, it was resistant to 1 μM but sensitive to 10 μM TRAM-34, a specific IKCa channel blocker. Furthermore, DCEBIO reduced the mitochondrial membrane potential by opening IKCa channels.
<>Therefore, DCEBIO should increase myotube mass by opening of IKCa channels distributed in mitochondria. Pharmacological studies revealed that mitochondrial reactive oxygen species (mitoROS), Akt, and mammalian target of rapamycin (mTOR) are involved in DCEBIO-induced myotube hypertrophy. An additional study demonstrated that DCEBIO-induced muscle hypertrophic effects are only observed when applied in the early stage of myogenic differentiation. In an in vitro myotube inflammatory atrophy experiment, DCEBIO attenuated the reduction of myotube diameter induced by endotoxin. Thus, we concluded that DCEBIO increases muscle mass by activating the IKCa channel/mitoROS/Akt/mTOR pathway. Our study suggests the potential of DCEBIO in the treatment of muscle wasting diseases. <>Significance Statement: Our study shows that 5,6-dichloro-1-ethyl-1,3-dihydro-2H-benzimidazol-2-one (DCEBIO), a small molecule opener of Ca2+-activated K+ channel, increased muscle diameter via the

mitochondrial reactive oxygen species/Akt/mammalian target of rapamycin pathway. And DCEBIO overwhelms C2C12 myotube atrophy induced by endotoxin challenge. Our report should inform novel role of K+ channel in muscle development and novel usage of K+ channel opener such as for the treatment of muscle wasting diseases.[57.3]

[C] Sodium Ions & Potassium Ions are necessary for muscle endurance. Electrolytes are therefore some of the most beneficial essential nutrients to promote athletic performance intra-competition, if the dosages of the electrolytes consumed by athletes are adequate and not trivial such as contained within overpriced Sports Drinks.

"<>Intensive contractile activity is associated with a significant net loss of K+ and a comparable gain of Na+ in the working muscle fibres. This leads to an increase in the interstitial and T-tubular K+ concentration and to a decrease in the T-tubular Na+ concentration. It is well established that the exposure of muscles to high extracellular K+ or low extracellular Na+ inhibits contractile performance.
<>More importantly, the combination of high extracellular K+ and low extracellular Na+ has a much more pronounced inhibitory effect on force than the sum of the individual effects of the two ions. The inhibitory effects of high extracellular K+ or low extracellular Na+ can be alleviated within 5-10 min by acute hormonal stimulation of the Na+, K+ pump. In contrast, reductions in the capacity for active Na+, K+ transport by pre-incubation of isolated muscles with ouabain or by prior K+ depletion of the animals significantly decreases contractile endurance during high-frequency electrical stimulation.
<>Thus, muscles from K(+)-depleted rats exhibiting a 54% reduction in Na+, K+ pump concentration showed a 110% increase in force decline during 30 s of 60 Hz stimulation. Reducing the Na+, K+ pump capacity to a similar extent by pre-incubation with ouabain led to a comparable decrease in endurance. Moreover, reductions in the Na+, K+ pump capacity were associated with an increased intracellular accumulation of Na+ during electrical stimulation. These observations support the notion that excitation-induced decreases in Na+, K+ gradients contribute to fatigue during intensive exercise and suggest that the capacity for active Na+, K+ transport is a determining factor for contractile endurance."[57.4]

Myofibrils, Sarcomeres, & Costameres

Myofibrils

Myofibrils are what make up a myofiber (muscle fiber), they are small tube-like structures. Myotubes form first during myogenesis, but they do not contain the myofibrils necessary for muscle contraction, hence the need for detraining, to allow myotubes to synthesize the proteins necessary to develop myofibrils.

"<>Individual myofibrils are approximately 1 μm in diameter and comprise approximately 80% of the volume of a whole muscle. The variable number of myofibrils is regulated during the hypertrophy of muscle fibers that is associated with growth; for example, the number of myofibrils ranges from 50 per muscle fiber in the muscles of a fetus to approximately 2000 per fiber in the muscles of an untrained adult."[58]

Sarcomeres

Put succinctly:

"<>A sarcomere is the basic contractile unit of muscle fiber (myofibril). Each sarcomere is composed of two main protein filaments—actin and myosin—which are the active structures responsible for muscular contraction. The most popular model that describes muscular contraction is called the sliding filament theory. In this theory, active force is generated as actin filaments slide past the myosin filaments, resulting in contraction of an individual sarcomere."[59]

We can think of a myofiber as a train, a pliable train that can elongate or compress, that is filled with (interior but pictured as exterior) lattice-like Z-Discs and M-Lines, these are reinforcement to the trains structure, these longitudinal lattices are responsible for the conformational changes that myofibers experience when shortening or lengthening through mechanotransduction. Myosin heads are to be considered workers who stand adjacent to the train, who when given the signal (being exposed to ATP & Calcium Ions) begin to pull the train across the track by rope, this is the formation of crossbridges with the Actin Filaments (Train Tracks) and Myosin Heads (Train Workers), thus creating a "power stroke", or muscle contraction.

Importantly, when these Myosin Heads connect to Actin, they compress a Myofibril, and this movement pattern is a longitudinal axial rotation, a leftward motion, such that the Myofibril Train is compressed by way of the Myosin Head Train workers, wherein it moves along the Actin Filament Train Tracks, which are anchored or supported by Costameres above.

Costameres

[A] Costameres are essential for myofibril attachment & muscle force production.

Myofibrils are interconnected through Costameres, which are functional components which connect the sarcomere to the cell membrane. These are another essential component of muscle force production. Similarly to Myosin Heads, they move during muscle contraction, their purpose is protect myofibrils from excessive conformational changes by connecting a Myofibril to the Extracellular Matrix, they are to be considered flexible anchors that maintain the stability of the train track visualized as overhead support systems (Actin Filaments). Costameres are vital for the maintenance of Myofibril structure and the crossbridging that occurs during muscle contraction, they move in

response to the conformational changes Myofibrils experience during muscle contraction, preventing excessive deformation, & maintaining tension (force) during Myosin Head crossbridging.

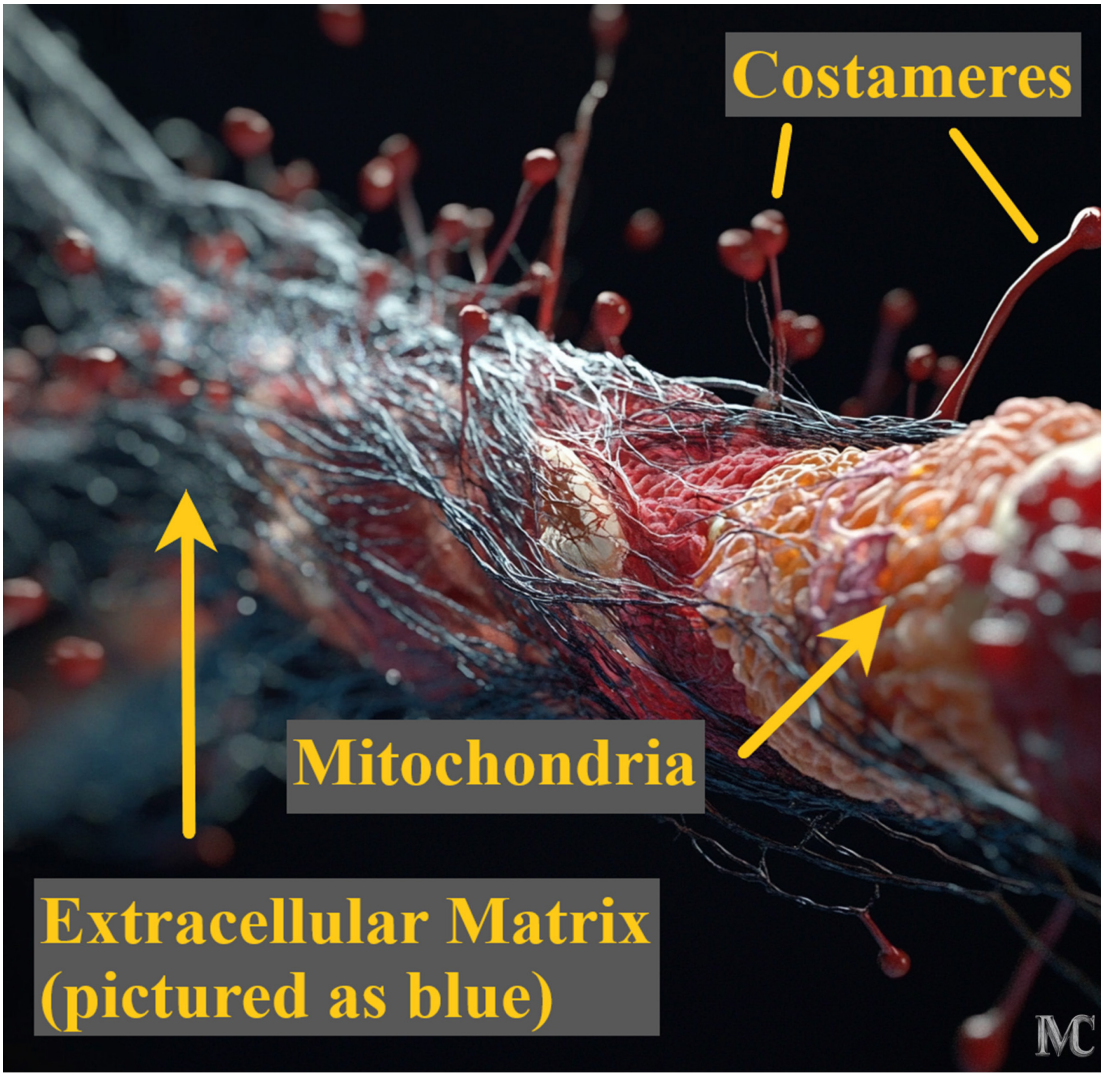
Pictured on the previous page is a more realistic representation of a Myofibril with Costameres attached, not to be confused with a Muscle Fiber. Interestingly, Mitochondrion are located between Myofibrils.

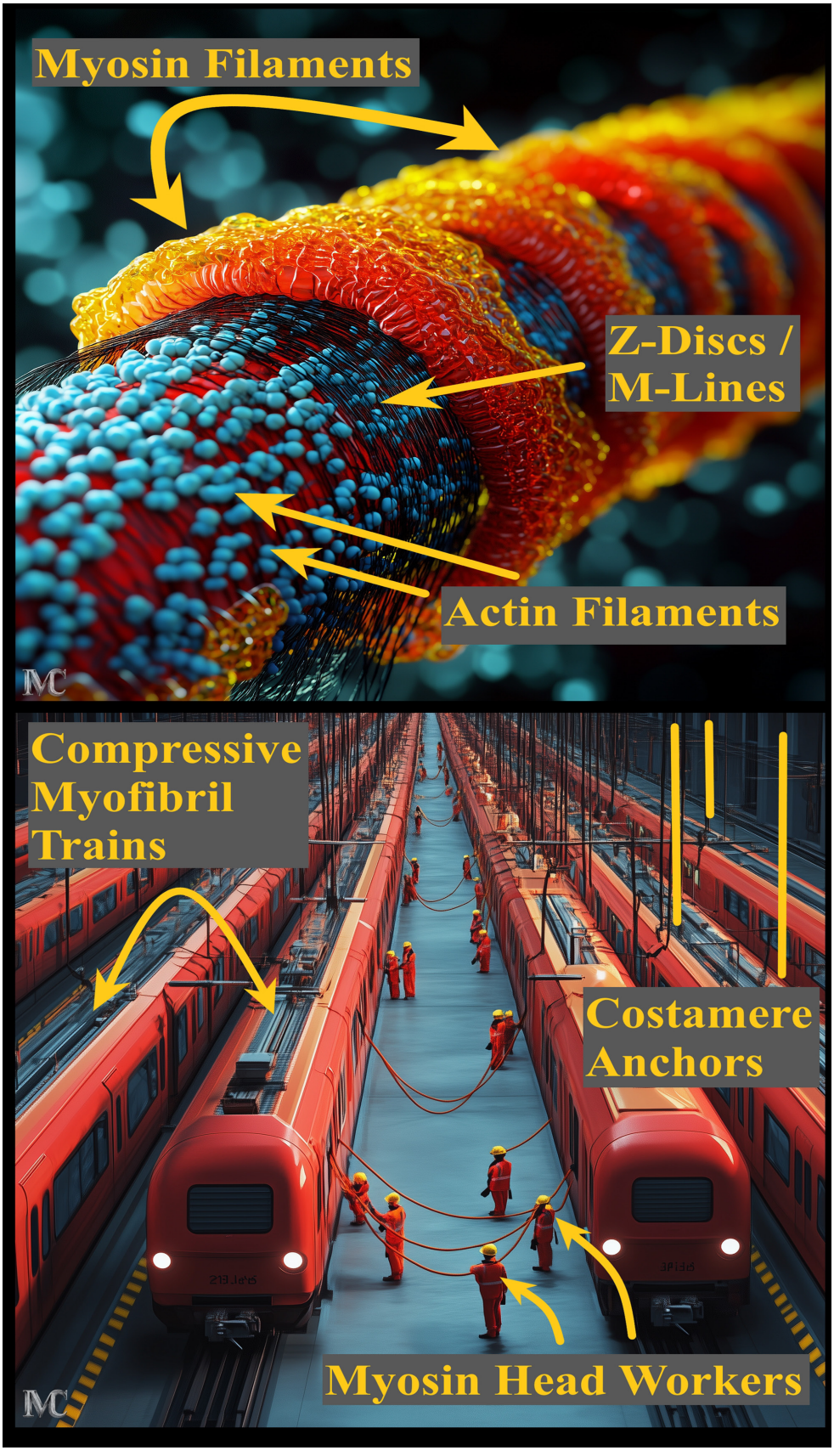
"<>The mechanical force we use to move our bodies is generated by the contraction of skeletal muscle fibers, while at the same time our hearts keep pumping blood through our circulatory system by way of cardiac muscle contraction. At the ultrastructural level, the force necessary for both cardiac and skeletal muscle contraction is generated by the shortening of individual sarcomeres. Force transmission in muscle can occur either parallel to or lateral to the long axis of the sarcomere.
<>In the longitudinal direction, force is transduced from one sarcomere to the next within the same fiber until the end of fiber is reached. Perpendicular, or lateral force transmission, allows for transduction from one myofibril to a neighboring myofibril until it reaches the costameric complex which channels the intracellular force across the sarcolemma to the extracellular matrix (ECM).
<>Recent experiments have shown that longitudinal force transmission accounts for only 20– 30% of force generated by sarcomeres, indicating that the major force vector occurs laterally within striated muscle. This suggests that the location of the costamere makes it critical for its central role in force transmission. Moreover, signals which produce physiological or pathological growth of myocytes following alterations of mechanical load are received by the cellular membrane and subsequently transmitted to subcellular domains including costameres."[60]

[B] Costameres participate in mechanical load-induced growth. As muscle hypertrophy proceeds, Costameres participate in the connection of newly formed myofibrils within a preexisting muscle fiber network, not to be confused with myogenic hyperplasia, wherein wholly new myotubes are formed, which contain new myofibrils. This is another separation between Early and Secondary Hypertrophy, where Myofibrillogenesis occurs within 24-48 Hours after exercise, Hyperplasia occurs in the following 72-96 hours. If we understand that Early Hypertrophy, and by proxy, early wound healing, require Pro-Inflammatory factors to initiate and successfully mobilize stem cells following muscle injury (exercise), then it could be hypothesized that the plateau we all reach when overtraining, when we no longer experience muscle growth, could be a direct result of insufficient pro-inflammatory factors, but this is just an idea of mine.

"<>Costameres are mechano-sensory sites of focal adhesion in the sarcolemma that provide a structural anchor for myofibrils. Their turnover is regulated by integrin-associated focal adhesion kinase (FAK). Because myofibrillar mass largely contributes to total protein that serves as a reference for the estimation of total protein content, the

increase in myofibrils with hypertrophy may camouflage (or dilute) any effect of resistance training on the amount of FAK.
<>As a consequence, the absence of a significant increase in the concentration of structural components of costameres with bedrest may indicate that their expression is affected, yet this does not manifest at the level of content vs. total protein. Conversely, hypertrophy induced by resistance training could have been expected to result in a reduction of the concentration of costameric proteins. However, we detected an increase, which further emphasizes that expressional adjustments of costameres are load-dependent.
<>Taken together, these observations indicate that a possible structural reinforcement of costameres in the late phase of muscle hypertrophy contributes to the attachment of newly synthesized myofibrils after the integrin anchor is laid down."[61]




Myosin Filaments
Z-Discs /
M-Lines
Actin Filaments
Compressive
Myofibril
Trains
Costamere
Anchors
Myosin Head Workers

Mitochondria

Mitochondria are the energy factories of our cells, they are essential components of conscious lifeforms, and intricately involved in evolution. Mitochondria are capable of growing through mitochondrial fusion or splitting apart during mitochondrial fission. Mitochondrial Fusion is a process wherein smaller mitochondria fuse to form larger mitochondria networks, most often associated with ROS exposure (Mitohormesis), and is beneficial towards physical and neurological health.

Mitochondrial Fission is the process of mitochondrial breakdown, of mitochondrion dividing into two or more smaller daughter mitochondria. This can be beneficial to degrade damaged mitochondria through Mitophagy, a process wherein damaged mitochondria are degraded by autophagosomes, which recycle mitochondrial components (Amino Acids, Fatty Acids, etc.). Mitochondrial Fission is a result of Mitophagy and may become pathological and therefore promote physical and neurological aging if it is uncontrolled, but it is a necessary result of the targeted breakdown of damaged mitochondria.

Mitochondrion form networks which must be balanced by the adaptive processes known as Fusion and Fission, if one process is uncontrolled it can result in damage or death to a cell. The most common form of cellular damage occurs when Mitochondrial Fission becomes hyperactive, such as in the development and pathology of numerous neurodegenerative conditions. Mitochondrial Biogenesis, if regulated by concurrent and effective Mitophagy will significantly delay cellular aging.

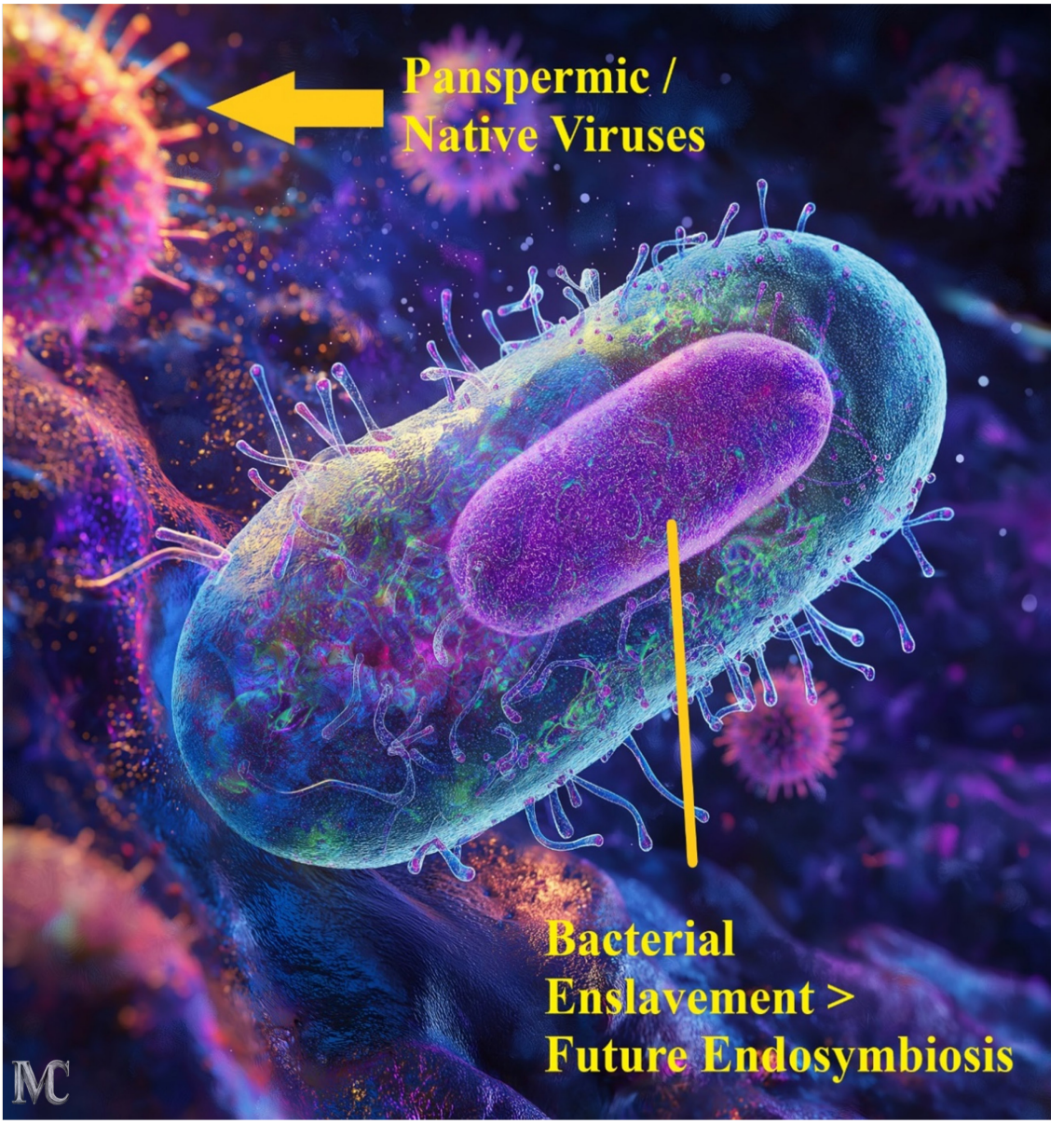
As pictured previously in the Costameres section, Mitochondria exist on Myofibrils, which are the contractile units contained within a muscle fiber. The decreased presence of Mitochondria within fast twitch muscle fibers is likely to be one reason for the rapid atrophy that they experience during unloading, this would therefore be one explanation for why absolute strength (power) is so difficult to maintain.

The Endosymbiotic Theory of Mitochondrial Evolution

Mitochondria evolved through the “permanent intracellular enslavement of photosynthetic bacteria” billions of years ago, which resulted in a symbiosis forming over time[1]-[2]. Simply explained: An ancient eukaryotic cell called an alpha-proteobacteria engulfed (attempted to digest) a neighboring aerobic bacterial cell, and due to being resistant to digestion, the bacterial cell survived. As a result of this, over the course of millions of years, the aerobic bacterial cell began to provide the eukaryotic cell with a new source of energy called aerobic respiration, which is when cells derive energy from oxygen by converting it into ATP. Eventually this engulfed cell transformed through genetic integration (horizontal gene transfer, likely mediated by viral infection, or parasitic infection), co-evolution, and specialization, into what we know of as today, Mitochondria.

The prime candidate for the bacteria that became mitochondria are the parasites Rickettsiales, which if proven true means that it was not “enslavement” of neighboring

bacteria that initiated Endosymbiosis, but instead, symbiotic infection. So too would ancient viruses have played a role in the evolution of ancient microorganisms through a process called **Virus-mediated Horizontal Gene Transfer** where ancient viruses through high frequency infection gave microorganisms *new* genes or altered preexisting genes. Innumerable infections were therefore necessary to facilitate—to mutate us into what we are today. These viruses could logically only have come from space, which is currently theorized as Panspermia, See: Panspermia & Viruses for more information on the nature of viruses versus traditional organic life.



Although it also argued that a *purple* bacterium such as Rhodobacteraceae was responsible for Endosymbiosis, considering it is highly symbiotic, and photosynthetic.

Regardless, I found it puzzling how both bacterial species debated to be the ancestors of mitochondria share many similarities to human mitochondria, one being parasitic and one being symbiotic (prior to enslavement). This has led me to the following hypothesis:

The Predator-Prey Endosymbiont Hypothesis

It is my hypothesis that these ancient alpha-proteobacteria engulfed multiple different neighboring bacteria, whether they were parasitic or symbiotic, which lead to simultaneous Endosymbiological evolution, thus explaining the evolutionary diversity of species, especially the clear distinction between predatory-carnivorous lifeforms, ones with evolutionarily parasitic mitochondria progenitor cells, and herbivorous / omnivorous lifeforms, ones with evolutionarily symbiotic / chemotrophic mitochondria.

It makes more sense to me to suggest that predatory animals or parasitic microorganisms that inhabit our planet currently have evolved specialized forms and functions that are dependent on inherited parasitic genes. This hypothesis connects the gap between the Parasitism-to-Predation Theory and species diversification through inherited parasitic (predatory) or symbiotic traits.

Mitochondrial Dynamics

Mitochondria are capable of either Fission or Fusion, depending on many factors present in the body, such as AMPK, or the lack thereof[3]. Mitochondrial Fusion generally enhances lifespan and neurological health whereas excessive Mitochondrial Fission shortens lifespan and facilitates neurodegeneration[4].

Steady-state Cardiovascular exercise (SSC) is a necessary form of exercise to engage in to delay aging through physical and neurological Mitochondrial Biogenesis, whereas in my opinion, high load resistance training serves the role of preparing the muscles through growth for continued cardiovascular conditioning.

[1] "<>Life on earth has existed for around 4 billion years. For the first 2 billion, all creatures alive were single cells with no nucleus. Then—according to a leading theory (Martin & Müller, 1998; Martin, Neukirchen, Zimorski, Gould, & Sousa, 2016)—certain bacteria invaded certain archaea, members of a separate domain of microbes. At the time, these archaea lived around volcanic ridges on the ocean floor and fed on carbon dioxide and on hydrogen from submarine hydrothermal vents. The bacteria lived in the vicinity, fed on organic compounds, and discharged as waste products precisely the carbon dioxide and hydrogen that the archaea made use of. Microbes do sometimes break into one another, and the result is rarely a happy marriage.
<>After tolerating the bacteria for a while, however, the invaded archaea evolved to take advantage of them and ended up integrating them for good. In the process, the bacteria became mitochondria, the milk cows of their hosts, and shed most of their genetic material. Thanks to their new milk cows, the hosts had plenty of energy ready for use and could afford to pick up parts of the discarded material, build a kind of control center out of it—a cell "nucleus"—and evolve from prokaryotes (organisms made of one cell with no

nucleus) into eukaryotes (organisms made of one or more cells with a nucleus, like us).”[61.1]

[2] “<>First discussions of the symbiogenetic origin of mitochondria from purple non-sulphur bacteria assumed that the host was anaerobic, and that the symbiont was an aerobically respiring heterotroph, enslaved because of the greater efficiency of ATP production by oxidative phosphorylation that it provided for the first time. However, it is more likely that host and symbiont were both facultative aerobes; if the host already had oxidative phosphorylation, the ultimate selective advantage was greater efficiency derived from respiratory and metabolic compartmentation.
<>I now argue that the immediate selective advantage for initial enslavement would have been far stronger if the symbiont were not heterotrophic, but photosynthetic instead, with immediate intracellular synergy between a respiring and phagotrophic host (using oxygen and excreting CO2) and a photosynthetic symbiont fixing that CO2 (as in intracellular photosynthetic dinoflagellates in corals).
<>Many photosynthetic microbes exude photosynthesate into the medium: marine phytoplankton excrete 1–40% of total photosynthesate, cyanobacteria secrete vitamins, and α-proteobacteria secrete glycollate under aerobic conditions, suggesting that a photosynthetic intracellular ancestor of mitochondria could have established a synergistic symbiosis with host peroxisomes analogous to that in plant photorespiration where glycollate exuded by plastids is recycled by peroxisomes. <>Intracellularly cultivating such a strain would immediately benefit the host even prior to the difficult evolution of protein import into it, unlike in the classical heterotrophic symbiont theory. Once mutualistic endosymbiosis was established, mutations giving the consortium a reproductive advantage would be selected. This scenario is plausible, as photosynthetic purple non-sulphur bacteria endosymbiotic in eukaryotic hosts are known.”[61.2]
[Truncated]

[3] “<>The basics of mitochondrial structure: Mitochondria are dynamically interconnected, allowing them to share membranes, solutes, metabolites and proteins, as well as electrochemical gradients. Each mitochondria is organized into two phospholipid bilayers: the outer mitochondrial membrane (OMM), which separates the intermembrane space from the cytosol, and the inner mitochondrial membrane (IMM), which forms cristae into the matrix. While the OMM is mostly permeable to ions and larger molecules, the IMM is less so. Across the IMM an electrochemical gradient is formed, allowing ATP formation through oxidative phosphorylation, heat production through proton leaking, and ROS formation through oxygen reduction.”
“<>Fusion and fission proteins and processes: Fusion occurs when two adjacent mitochondria join, while fission separates one mitochondria into two. These two events permanently counterbalance each other; the inactivation of one leads to unopposed action by the other and the subsequent imbalance controls mitochondrial structure.
“<>Generalized and simplified summary of the main pathways linking nutritional state with mitochondrial dynamics and their ultimate phenotypic outcome. AMPK, insulin/IGF, and mTOR nutrient signaling pathways constitute a core network in

mammalian cells to coordinate metabolism and regulate lifespan. Depending on the availability of nutrients, these signaling pathways are differentially switched on or off, corresponding to specific mitochondrial morphologies. For example, under the condition of starvation, AMPK is activated, while insulin/IGF and mTOR signaling are suppressed. This change typically favors mitochondrial fusion, which is associated with major beneficial effects such as prolonged lifespan, improved insulin sensitivity, and enhanced glucose tolerance. In contrast, nutrient excess activates insulin/IGF and mTOR signaling but represses AMPK. This leads to an activation of mitochondrial fission, which is associated with a number of human pathologies such as aging, cardiomyopathy, obesity, and diabetes. It should be noted that these responses are not uniform and are highly context-dependent."

↓ Continued:

[4] "<>Abnormal, fragmented mitochondrial networks have been implicated in many other neurodegenerative diseases that are not primarily caused by mutations in fission- or fusion-related genes, such as Parkinson's disease (PD), Alzheimer's disease (AD), and Huntington's disease (HD). For example, loss of PINK1 or Parkin in human SH-SY5Y cells, associated with PD, results in excessive mitochondrial fragmentation mediated by DRP. Blocking the fission process attenuates dopaminergic neuronal degeneration and restored striatal dopamine release in both a PINK1 deletion PD mouse model and an environmental PD mouse model. In addition, beta-amyloid, believed to be the primary cause of Alzheimer's disease, increases neuronal nitric oxide, which triggers mitochondrial fragmentation and neuronal damage by activating DRP1 through S-nitrosylation. Consistent with this observation, the level of S-nitrosylated DRP1 is also elevated in brains of human AD, suggesting mitochondrial fragmentation as a contributor to the pathogenesis of AD. Accordingly, inhibiting mitochondrial fission pharmacologically alleviates beta-amyloid-caused neuronal apoptosis. In addition, Tau and mutant huntingtin were shown to directly interact with and activate DRP1, consequently augmenting fission and sensitizing neurons to apoptosis observed in patients with HD or AD. <>Collectively, these data highlight mitochondrial fragmentation as an important contributor to the pathogenesis of these neurodegenerative diseases and suggest that restoring homeostasis of mitochondrial morphology genetically and/or pharmaceutically is a potentially viable and appealing therapeutic strategy to treat these diseases."

"<>Mitochondrial morphology reacts to distinct metabolic cues. A growing body of evidence suggests that mitochondrial network dysfunction is tightly associated with metabolic disorders including obesity, insulin resistance, and diabetes. For example, in obese Zucker rats and obese humans, skeletal muscle mitochondria are smaller and fragmented."[61.3] [Truncated]

[A] Redox Reactions describe the changing of electrons between molecules to produce ATP, this process is called Cellular Respiration. ROS are produced in mitochondria, primarily as a result of *Electron Leakage* that occurs during Cellular Respiration (Cellular Respiration = Mitochondrial Macronutrient Metabolism = Beta-oxidation: See: Lipolysis), while a smaller percentage of Mitochondria-generated ROS come from

cellular toxins such as heavy metals or other chemicals, or from Mitochondria that have become damaged through aging and leak an excess amount of Electrons during metabolic processes. These cellular generated ROS are capable of diffusing, or escaping, from the Mitochondria and spreading to other cells.

Macronutrients (Carbohydrates, Protein, Fatty Acids) are converted during digestion and metabolism into Acetyl-CoA molecules, which are further refined into the battery-like molecules NADH & FADH2 in the Citric Acid Cycle, which are sent into the Electron Transport Chain where they donate their electrons to a Proton Pump, which charges the Proton Gradient, which fuels the activation of ATP Synthase, which produces ATP molecules from leftover ATP breakdown products (ADP / Pi). For a visual representation of this refer to the section: Lipolysis.

"<>Mitochondria have a myriad of essential functions including metabolism and apoptosis. These chief functions are reliant on electron transfer reactions and the production of ATP and reactive oxygen species (ROS). The production of ATP and ROS are intimately linked to the electron transport chain (ETC). Electrons from nutrients are passed through the ETC via a series of acceptor and donor molecules to the terminal electron acceptor molecular oxygen (O2) which ultimately drives the synthesis of ATP. Electron transfer through the respiratory chain and nutrient oxidation also produces ROS. At high enough concentrations ROS can activate mitochondrial apoptotic machinery which ultimately leads to cell death.
<>However, if maintained at low enough concentrations ROS can serve as important signaling molecules. Various regulatory mechanisms converge upon mitochondria to modulate ATP synthesis and ROS production. Given that mitochondrial function depends on redox reactions, it is important to consider how redox signals modulate mitochondrial processes.
<>Here, we provide the first comprehensive review on how redox signals mediated through cysteine oxidation, namely S-oxidation (sulfenylation, sulfinylation), S-glutathionylation, and S-nitrosylation, regulate key mitochondrial functions including nutrient oxidation, oxidative phosphorylation, ROS production, mitochondrial permeability transition (MPT), apoptosis, and mitochondrial fission and fusion. We also consider the chemistry behind these reactions and how they are modulated in mitochondria. In addition, we also discuss emerging knowledge on disorders and disease states that are associated with deregulated redox signaling in mitochondria and how mitochondria-targeted medicines can be utilized to restore mitochondrial redox signaling."[61.3.1]

[B] Cardiovascular exercise promotes Mitochondrial Biogenesis in the bran.

"<>Increased muscle mitochondria are largely responsible for the increased resistance to fatigue and health benefits ascribed to exercise training. However, very little attention has been given to the likely benefits of increased brain mitochondria in this regard. We examined the effects of exercise training on markers of both brain and muscle

mitochondrial biogenesis in relation to endurance capacity assessed by a treadmill run to fatigue (RTF) in mice. Male ICR mice were assigned to exercise (EX) or sedentary (SED) conditions (n = 16-19/group).
<>EX mice performed 8 wk of treadmill running for 1 h/day, 6 days/wk at 25 m/min and a 5% incline. Twenty-four hours after the last training bout a subgroup of mice (n = 9-11/group) were euthanized, and brain (brain stem, cerebellum, cortex, frontal lobe, hippocampus, hypothalamus, and midbrain) and muscle (soleus) tissues were isolated for analysis of mRNA expression of peroxisome proliferator-activated receptor-gamma coactivator-1-alpha (PGC-1α), Silent Information Regulator T1 (SIRT1), citrate synthase (CS), and mitochondrial DNA (mtDNA) using RT-PCR. A different subgroup of EX and SED mice (n = 7-8/group) performed a treadmill RTF test.
<>Exercise training increased PGC-1α, SIRT1, and CS mRNA and mtDNA in most brain regions in addition to the soleus ($P < 0.05$). Mean treadmill RTF increased from 74.0 ± 9.6 min to 126.5 ± 16.1 min following training ($P < 0.05$). These findings suggest that exercise training increases brain mitochondrial biogenesis, which may have important implications, not only with regard to fatigue, but also with respect to various central nervous system diseases and age-related dementia that are often characterized by mitochondrial dysfunction."[61.4]

[C] High intensity interval cardio training, *but not classical resistance training*, results in Mitochondrial Biogenesis. Although higher intensity higher load strength training, such as popularized by Mike Mentzer, and eventually Dorian Yates, will obviously result in greater changes to muscle mitochondria post-training, the risk of muscle injury renders this sort of "HIT" resistance training illogical, and unsustainable, as evidenced by their physiques after retiring (withdrawing from anabolic steroids).
It must be clarified that Interval Training is not drastically different from Steady-state Training, aside from the potential differential amount of Lactic Acid generated within skeletal muscles during training, and the programmed intra-exercise rest periods, they are indistinct.

"<>This study investigated how different exercise training modalities influence skeletal muscle mitochondrial dynamics. Healthy [average body mass index (BMI): 25.8 kg/m2], sedentary younger and older participants underwent 12 wk of supervised high-intensity aerobic interval training (HIIT; n = 13), resistance training (RT; n = 14), or combined training (CT; n = 11). Mitochondrial structure was assessed using transmission electron microscopy (TEM). Regulators of mitochondrial fission and fusion, cardiorespiratory fitness (V̇o2peak), insulin sensitivity via a hyperinsulinemic-euglycemic clamp, and muscle mitochondrial respiration were assessed.
<>TEM showed increased mitochondrial volume, number, and perimeter following HIIT ($P < 0.01$), increased mitochondrial number following CT ($P < 0.05$), and no change in mitochondrial abundance after RT. Increased mitochondrial volume associated with increased mitochondrial respiration and insulin sensitivity following HIIT ($P < 0.05$). Increased mitochondrial perimeter associated with increased mitochondrial respiration, insulin sensitivity, and V̇o2peak following HIIT ($P < 0.05$). No such relationships were

observed following CT or RT. OPA1, a regulator of fusion, was increased following HIIT ($P < 0.05$), whereas FIS1, a regulator of fission, was decreased following HIIT and CT ($P < 0.05$). HIIT also increased the ratio of OPA1/FIS1 ($P < 0.01$), indicative of the balance between fission and fusion, which positively correlated with improvements in respiration, insulin sensitivity, and $\dot{V}o2peak$ ($P < 0.05$).
<>In conclusion, HIIT induces a larger, more fused mitochondrial tubular network. Changes indicative of increased fusion following HIIT associate with improvements in mitochondrial respiration, insulin sensitivity, and $\dot{V}o2peak$ supporting the idea that enhanced mitochondrial fusion accompanies notable health benefits of HIIT.
<>NEW & NOTEWORTHY We assessed the effects of 12 wk of supervised high-intensity interval training (HIIT), resistance training, and combined training (CT) on skeletal muscle mitochondrial abundance and markers of fission and fusion. HIIT increased mitochondrial area and size and promoted protein changes indicative of increased mitochondrial fusion, whereas lessor effects were observed after CT and no changes were observed after RT. Furthermore, increased mitochondrial area and size after HIIT associated with improved mitochondrial respiration, cardiorespiratory fitness, and insulin sensitivity."[61.5]
[D] Mitochondria played an integral role in our evolution as detailed in this landmark paper, Martin Picarda, and Carmen Sandid discuss the origin and function of Mitochondria by compiling and summarizing the current research on mitochondria and explain the necessity of mitochondria in the development of consciousness, and our hypersocial nature as species.

"<>Mitochondria are small organelles that live within each cell of the human body. They are bacteria-derived, having evolved over a billion years ago from aerobic bacteria incorporated into the then unicellular ancestor of the eukaryotic cell. This endosymbiotic fusion made multicellular complex life possible – it gave rise to breathing, moving, thinking, feeling multicellular organisms with complex bodies like humans and other social creatures."

↓ continued

"<>Mitochondria exhibit several essential characteristics of social organisms. Below, we discuss six essential principles and how they manifest in mitochondrial behavior: (1) shared environment, (2) communication, (3) group formation, (4) synchronization of behavior, (5) functional interdependence, and (6) specialization and division of labor."

(1) Shared Environment:

"<>A shared environment is a distinctive feature of cultures and societies. In social groups living in a particular ecosystem, variation in habitat and diet are closely associated with the size and structure of the group (Clutton-Brock et al., 2009). When confined, a shared environment can largely determine individuals' characteristics. Darwin's finches or Galapagos tortoises, which shared distinct and confined environments in their evolutionary past, deviated in several characteristics from descendants of their common ancestors that lived in geographically more accessible areas, including the shape of their

beaks and shells (Hedrick, 2019). In humans also, geographical borders produce groups of individuals that differ in their behavior and beliefs (Onnela et al., 2011), and disparities in physical and mental health among ethnic minorities can emerge in geographically-defined ways (Alarcon et al., 2016).

<>Similarly, large networks of mitochondria – counted in 100-1000's when physically fragmented (Scheffler, 2008) – share the same immediate environment bound by the cell membrane. All members of the mitochondrial community within a given cell share the same cytoplasm, which includes information about the cell cycle stage, its differentiation status, activation state, and second-messengers from external stimuli as well as internal activities. Mitochondria within a given cell also share the same cell nucleus, which provides many of the gene products and proteins essential to harmonize mitochondrial behavior within the cell. Moreover, different organs are composed of specific cell types (e.g., neurons, cardiomyocytes, hepatocytes) that contain mitochondrial populations with distinct molecular compositions (Calvo et al., 2016). Thus, both social animals and mitochondria coexist in spatially-defined, shared environments that contribute to shape and preserve distinct populations of individuals, which engage in constant communication with each other."

(2) Communication:

"<>As described above in Section 2, communication is an essential element of social organizations. It is supported by multiple redundant mechanisms, enables both close and distant exchanges among social networks, and impairment in social communication alters healthy functioning of social groups.

<>Similarly, several redundant mechanisms exist to facilitate communication among mitochondria. Physical membrane structures called inter-mitochondrial junctions (Picard et al., 2015a) and mitochondrial nanotunnels (Vincent et al., 2017) physically connect mitochondria and enable information exchange while retaining individual organelle boundaries. A more complete mechanism towards molecular information exchange is the fusion of two (or more) mitochondria into larger ones, leading to the more complete mixing of individual properties from the fusing mitochondria. Like human interactions, mitochondrial fusion can either be long-lasting, or partial and brief (kiss-and-run) (Liu et al., 2009).

<>Moreover, through their life cycle, mitochondria are born from one another through the process of synonymous division (i.e., biogenesis), enabling the transmission of physical and functional properties (Scheffler, 2008) and possibly the propagation of a "trans-generational" memory. Chemical signals such as reactive oxygen species and calcium can also act as diffusible signals that transmit information without direct physical contact between mitochondria (Garcia-Perez et al., 2012).

<>As in human social networks and in brain neural circuits, the exchange of information among functionally networked mitochondria may enable groups of mitochondria to "perceive" incoming signals and respond as a collective unit, leading to some degree of signal integration within the mitochondrial network (Picard, 2015). Impairing communication among mitochondria by blocking mitochondrial fusion increases

molecular heterogeneity among the intracellular mitochondrial community (Chen et al., 2005), causes the accumulation of damage in the mitochondrial genome (Chen et al., 2010), and reduces the energy transformation potential of the mitochondrial population (Bach et al., 2003).

<>Moreover, these negative consequences reach beyond the malfunction of individual mitochondria and can lead to demise of the cell and of the organism during development (Chen et al., 2003). Moreover, mitochondria also communicate with other organelles through the exchange of soluble chemical signals at inter-organellar contacts, such as the endoplasmic reticulum (Csordas et al., 2018). Thus, communication is a shared principle that directly influences the behavior of both social animals and mitochondria."

(3) Group Formation:

"<>Groups are defined as a number of individuals or units that are related or located close to one another. Although not exempted from potential disadvantages (e.g., increased competition or higher rates of disease transmission) (Kappeler et al., 2015), the ubiquitous principle of aggregation (i.e., individuals living together in groups) in social animals generally provides substantial fitness advantages. Social aggregation and group living can help protect individuals from predatory threats (Krause and Ruxton, 2002), improve foraging efficiency (Pulliam and Caraco, 1984), and enhance individuals' ability to sense and respond to environmental changes (Berdahl et al., 2013). A key driving force determining which individuals come together is the similarity in their physiological capacities (e.g., aerobic capacity and fitness) (Killen et al., 2014; Seebacher and Krause, 2017).

<>Accordingly, the functioning as a group largely relies on the physiological underpinnings that determine how conspecifics perceive and process information from each other. Furthermore, inter-individual differences in energetic resources may affect patterns of motion and rest, determining different levels in fatigue resistance that, eventually, may contribute to passive or active sorting of social groups (Seebacher and Krause, 2017). Across evolution, social animals including humans have increased the size and complexity of groups (Dunbar and Shultz, 2007), highlighting in parallel with more complex forms of behavior the likely evolutionary advantage of group formation.

<>Within cells, mitochondria form groups that can differ in their fitness and topologically localize in different cellular compartments. As mentioned above, in cells with highly polarized morphology like neurons, different compartments such as the cell body (i.e., soma), dendrites, and axons have remarkably different populations of mitochondria. Somatic mitochondria vary in shape from spheroids to moderately elongated tubules; dendritic mitochondria exist as extremely long and branched stationary organellar networks; and axonal mitochondria are small motile units (Lewis et al., 2018). Mitochondria can cluster near the plasma membrane (Porat-Shliom et al., 2019), at cell-cell membrane contact sites (Gomez-Cabanas et al., 2019), around lipid droplets (Benador et al., 2018), or around the cell nucleus (Al-Mehdi et al., 2012) where they tend to aggregate with similarly behaving mitochondria and remain for the duration of their life cycle.

<>In cases of disease where specific mitochondria undergo changes in their capacity or behavior, mutant mitochondria also aggregate, forming functionally distinct groups (Vincent et al., 2018). As another example, young and old mitochondria with different fitness selectively segregate prior to cell division, such that young and old mitochondria are differentially passed on to distinct daughter cells (which impacts downstream cell fitness) (Katajisto et al., 2015). Thus, similar to humans and other social animals, functionally and morphologically similar mitochondria exhibit group behavior."

(4) Synchronization of behavior:

"<>Synchrony is essential to the lives of group-living organisms (Couzin, 2018) and is a vital phenomenon that manifests across all levels of biological complexity (Li and Yang, 2018). Synchronization serves multiple functions. For a group to stay cohesive, group members need to synchronize their activities, a phenomenon particularly relevant in animals during foraging and migration, where large groups migrate in unison (Seebacher and Krause, 2017). Synchronization facilitates information processing (Couzin, 2018) and allows rapid coordinated responses to threats (e.g., among a herd or swarm) (Noy et al., 2011).
<>In humans, collective behavior is a major principle in various contexts, from collective motion (e.g., coordinated team playing in group sports) and activity synchronization (e.g., dynamic movements in crowds), to decision making (Biro et al., 2016). In fact, humans have unique capacities for coordination – the orchestration of individuals activities in an orderly manner, and coordination is essential to several facets of human societies. Mother-infant synchrony is a guiding principle for the development of positive cognitive and behavioral outcomes among children (Leclere et al., 2014). Simple and repeated synchronous interactions between individuals are also responsible for creating complex adaptive group patterns (Sumpter, 2006). Multiple group-living social animals also exhibit highly coordinated collective patterns (e.g., global movements in a school of fish) believed to correspond to a form of biological self-organization (Couzin, 2009) resulting from the local interactions among individuals located in each other's immediate surrounding (Biro et al., 2016). <>The principles that support this type of self-organization include positive feedback, response thresholds, individual integrity, and variability that can lead to oscillatory behaviors (Sumpter, 2006). In the human body, coordinated processes manifesting as oscillations are also ubiquitous: a wide range of biological processes such as neuronal firing, heart beats, cell cycles, and circadian rhythms exhibit synchronized oscillatory behaviors (Li and Yang, 2018). In the brain, coordinated neuronal oscillations also allow for multiple-time-scale communication within and across neuronal networks (Buzsaki et al., 2013).
<>Similarly, in mitochondria, synchronized oscillations in membrane potential occur in cardiomyocytes where mitochondria are electrically coupled to one another (Aon and Cortassa, 2012; Kurz et al., 2010). In a different organ, the salivary gland, mitochondria communicate between cells through gap junctions and behave as a network of functionally coupled oscillators (Porat-Shliom et al., 2014). Spontaneous events of mitochondrial depolarization and rapid changes in superoxide levels, called "flashes",

also propagate at high speed between neighboring mitochondria – large groups of mitochondria flash synchronously (Santo-Domingo et al., 2013). Both membrane potential oscillations (Porat-Shliom et al., 2014) and flash propagation (Santo-Domingo et al., 2013) occur even when the mitochondria are not physically continuous with each other, pointing to the role of soluble signals for inter-mitochondrial communication. <>Moreover, the internal physical structure of mitochondrial membranes (i.e., the cristae) can also become coordinated at inter-mitochondrial junctions where two energized mitochondria are in close contact (Picard et al., 2015a), which may in part contribute to the functional coupling required for synchronization of behavior of juxtaposed mitochondria. Thus, synchronization of behavior is a shared principle extending from large groups of behaving animals to sub-cellular mitochondrial communities."

(5) Functional interdependence:

"<>Individuals from highly social species depend on one another for various aspects of their fitness (Aktipis et al., 2018; Silk, 2007b). Interdependence among social animals account for cooperation and altruism (Roberts, 2005), including unique forms of human cooperation (Tomasello and Gonzalez-Cabrera, 2017). By helping group partners, individuals are not only investing in their partners' fitness but also, consequently, in their own as well (Aktipis et al., 2018; Maynard Smith, 1964). Most social species limit their cooperative behaviors (i.e., acting for the common benefit of other individuals in the social group) to small groups frequently made up of relatives, and reciprocal interactions (Smaldino and Epstein, 2015). However, human societies can also reach extremely high levels of cooperative behavior, benefiting not only close relatives but also unrelated individuals. Examples of cooperative behavior in human societies range from the constructions of buildings and bridges to selfless actions such as charities and blood donations (Melis and Semmann, 2010). The latter type of actions, known as 'altruism' – the type of cooperative behavior directed to benefit other individuals at a cost to those that perform it – may be explained by its eventual (direct or indirect) fitness benefits for the individual that exerts the cooperative behaviors (Bourke, 2014; Hamilton, 1964a, b; West et al., 2007, 2006). <>Direct fitness may result when cooperation arises from the mutual dependence for survival or reproduction (termed fitness interdependence) (Aktipis et al., 2018), while indirect fitness arises when relatives are favored, increasing their reproductive success (Maynard Smith, 1964). From birth, humans are highly dependent on their caretakers. In this context, the establishment of early life attachment – a form of interdependence – between the infant and caregiver ensures optimal development and is essential for brain development, which determines long-term well-being (Sullivan et al., 2011). Globally, the spectrum of human activities embedded in human social networks progressively involves interdependent relationships, with billions of people now increasingly relying on each other for safety and the provision of various goods and skills.
<>At the subcellular level, fitness interdependence also accurately describes the relation between mitochondria and the cell nucleus: the nucleus requires mitochondria for energy and metabolic intermediates necessary for gene expression (Gut and Verdin, 2013), while

mitochondria depend upon the nucleus to generate most of their proteins that enable their multifarious nature (Calvo et al., 2016). Thus, mitochondria and nucleus depend on each other for their fitness and survival. Mito-nuclear signaling, which consist in the exchange of proteins and chemical signals between the mitochondrial population and the nucleus, shapes how the cell as a whole responds to stress and challenges (Cardamone et al., 2018; Nargund et al., 2012; Quiros et al., 2016). In addition, mitochondrial biogenesis and the associated changes in metabolism (i.e., from glycolysis to oxidative phosphorylation) can influence cell fate decision in neural stem cells, eventually affecting neurogenesis, and thereby having an impact in cognition (Arrazola et al., 2019).
<>Mitochondria also exist in a cooperative relationship with each other. This interdependence is most clearly observed in mitochondrial fusion and fission processes. Upon increased cellular energy demands or reduced energy supply, mitochondria fuse to increase effectiveness (Gomes et al., 2011; Rambold et al., 2011). Exercise also increases the number of physical contacts between mitochondria in skeletal muscles (Picard et al., 2013a). Importantly, as described in the section on mitochondrial communication, perturbing mitochondrial fusion eventually leads to the accumulation of mtDNA defects and the demise of the cells (Chen et al., 2010), revealing the essential nature of fusion-type cooperative mitochondrial interactions. Conversely, new mitochondria arise from previously established ones via the reciprocal process of fission. When intracellular calcium rises during cell stimulation, mitochondria act as calcium buffer and their ability to buffer calcium is significantly enhanced by their interactions with each other in the fused state (Paltauf-Doburzynska et al., 2004). Larger populations of mitochondria also naturally have greater calcium buffering capacity (Bianchi et al., 2006), consistent with the notion that mitochondria cooperate to handle cytoplasmic environmental challenges. Genetically, mitochondria also functionally complement each other. Isolated mitochondria without a genome or with a mutant genome can be rescued by fusing with healthy conspecifics, restoring their normal function and ensuring overall mitochondrial population health (King and Attardi, 1989; Ono et al., 2001). <>Furthermore, as evidence that mitochondrial physical interactions influence the behavior of the cells that contain them, mitochondrial dynamics influence neurogenesis within the brain (Khacho et al., 2016, 2017). Therefore, as for social animals, normal and optimal mitochondrial function is achieved through cooperative interactions among conspecifics, such that mitochondria exist as cooperative and functionally interdependent organelles."

(6) Specialization and division of labor:

"<>In many social species, high levels of inter-individual variation are optimal to enhance efficiency in solving the problems the group may be facing (Farine et al., 2017; Jolles et al., 2017). From social arthropods (Holldobler and Wilson, 1990) to humans (Agryris, 1973), within-group structural and functional variation enhances task efficiency and fitness (Pruitt and Riechert, 2011). A more deliberate form of functional variation is specialization: specific individuals within a population perform particular tasks, and develop tailored abilities or constitutions to optimally perform specific task(s). Division of labor is one of the hallmarks of social living. The extraordinary human capacity for

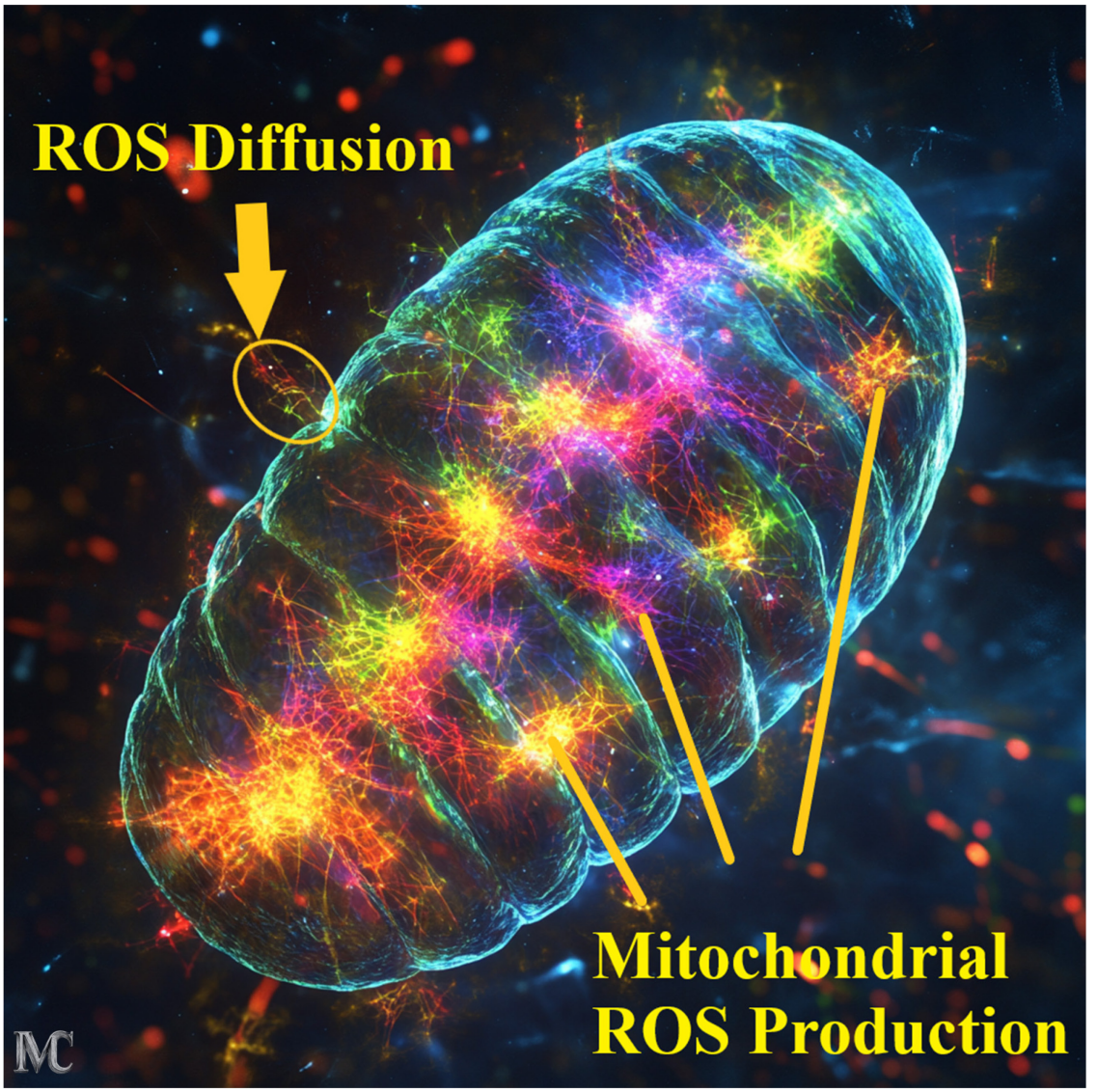
division of labor is a defining characteristic of all forms of organization in our societies. It manifests as the specialization in the performance of particular social roles, professions, and division of activities, followed by the subsequent exchange of products among social members. In economics, division of labor is also considered essential for the wealth of nations (Rosenberg, 1965).
<>Across the organism, functionally and molecularly specialized mitochondria acquire characteristics that allow them to perform specific tasks necessary for survival. Tissues with highest energetic demands, like the heart, contain dense mitochondrial populations with proteome and internal anatomy (dense cristae) optimized for energy transformation and ATP synthesis (Johnson et al., 2007; Piquereau et al., 2010). In the adrenal glands, mitochondria are morphologically distinct and specialize not in energy production, but in steroid hormone synthesis (Midzak and Papadopoulos, 2016). Thus, across the organism, organ systems, and cell types, mitochondria assemble in groups that perform specific tasks or labor that complement each other and are essential to the functioning of the whole body (Picard et al., 2018a). For example, heart and brain mitochondria require steroid hormones for their normal maturation, but the production of these hormones is outsourced to adrenal and gonadal mitochondria that specialize in steroidogenesis.
<>Even within single cells, distinct groups of perinuclear, peridroplet, and synaptic mitochondria differ in composition and morphology (see Section 3.3. Group formation). For example, neuronal mitochondria located either in the cell body and in synapses differ substantially from somatic mitochondria in their protein composition (Stauch et al., 2014), marking their distinct molecular identity and functional specialization. In other cell types, such as skeletal muscle fibers, mitochondria also exist as either globular mitochondria near the nucleus, or as long tubular mitochondria optimized for energy production located among contractile myofibrils (Picard et al., 2013b; Vincent et al., 2019).
<>Functionally, specialization and division of labor ensures that different groups of mitochondria are optimized and matched to the specific cellular environment they inhabit (Benard et al., 2006; Picard et al., 2012). Physiologically, several metabolites related to mitochondrial metabolism are produced by certain organs, and consumed by other ones, highlighting the systemic division of metabolic labor that interconnects organ-specific mitochondria as an interdependent network (Jang et al., 2019).
<>Thus, similar to humans and other social animals who develop unique set of behaviors and outsource others based upon immediate environmental demands, different groups of mitochondria distributed across the organism functionally specialize and divide labor, enabling complex organismal functions."[61.6]

Mitohormesis

Reactive Oxygen Species (ROS) when intermittently active within a cell or when active in low concentrations within a cell increase their resiliency by activating cellular defense processes, such as mitochondrial biogenesis, or natural antioxidant responses such as the activation of the protein Nuclear factor erythroid 2–related factor 2 (Nrf2), which

promotes the release of exogenous antioxidants such as superoxide dismutase, catalase, & glutathione. This is referred to as *Mitohormesis* and is an evolutionary advantageous and essential process required for cellular growth and survival. Conversely, when ROS rise to a high level, and remain elevated, they begin to cause mitochondrial and other intracellular component toxicity and promote aging through accelerated cellular senescence or cellular apoptosis. There are many different ROS molecules, and each ROS molecule will theoretically exert differential adaptive and destructive effects on a cell, similarly to essential nutrients.

In the distant future, athletes may be able to increase or decrease the concentrations or activity of specific ROS to promote or reduce specific cellular effects, such as for the purposes of *targeted mitohormesis*.



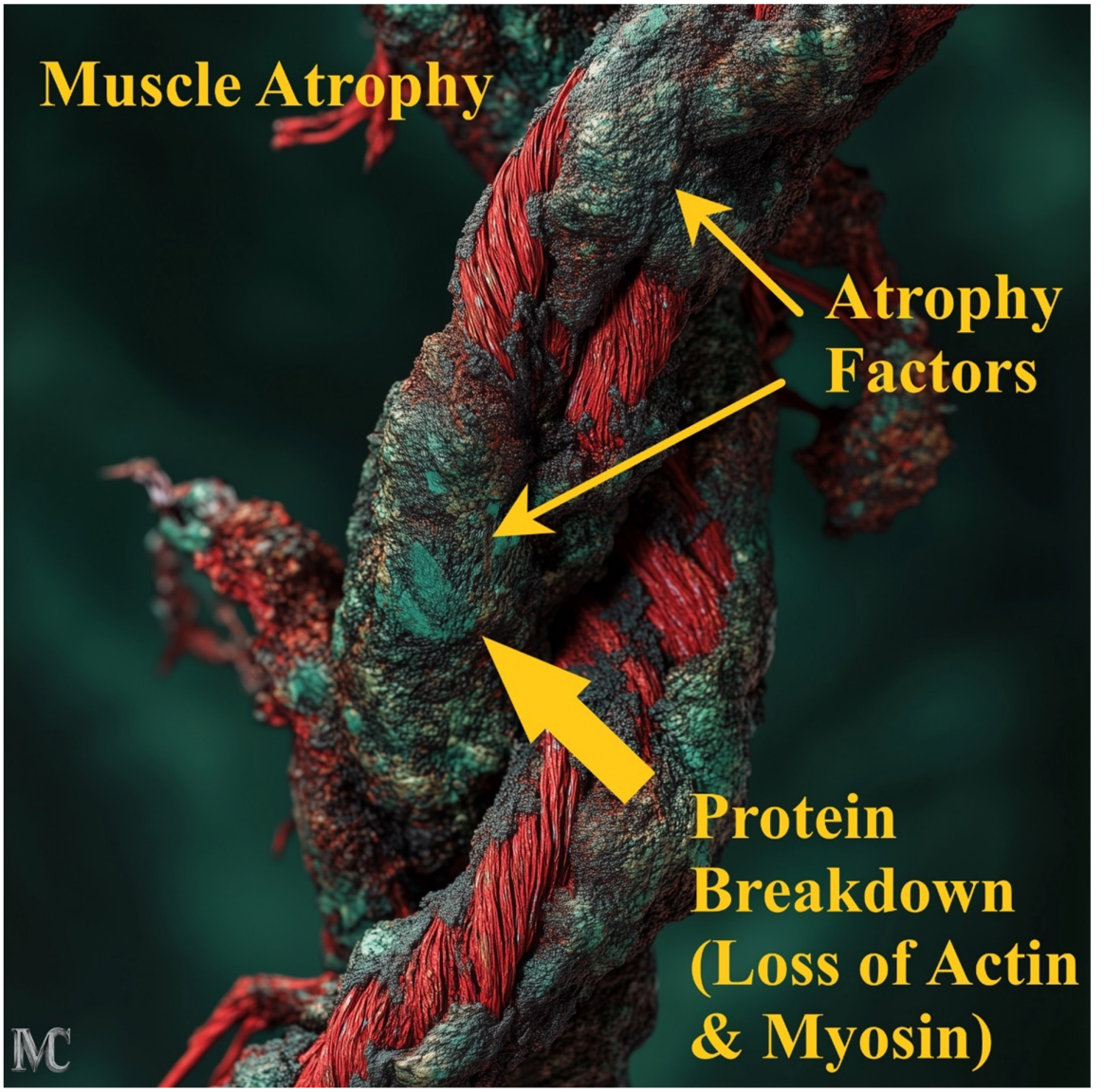
“<>Mitochondrial homeostasis is dependent on dynamic processes such as fusion, fission and removal of irreversibly damaged mitochondria (mitophagy), preventing the accumulation of dysfunctional organelles. However, mitophagy must be counter-balanced by mitochondrial biogenesis, allowing tuning mitochondrial function to the cellular needs. Indeed, signaling pathways activated by physiological stimuli such as changes in nutritional availability and energy requirements coordinate adaptive changes in oxidative metabolism mediated by a crosstalk between the nucleus and mitochondrial genomes.”
“<>A mitohormetic response is proposed to be triggered by transient mitochondrial stress wherein low, non-cytotoxic concentrations of ROS can serve as signals to mitochondrial and antioxidant signaling pathways promoting changes in the antioxidant defense system and mitochondrial dynamics, therefore resulting in extended lifespan.”
“<>A mild insult to a cell's mitochondrial population (such are, for example, small bursts of oxygen and nutrient deprivation, extremely low doses of mitochondrial inhibitors/toxicants) is a conditioning stimulus for the removal of older, less functional, more susceptible mitochondria from the population pool, allowing it to be repopulated by the generation of new, unharmed (biogenesis) mitochondria. However, if this insult is too prolonged or highly harmful, or if the cell has an inherent condition (for example, aged mitochondria with a lower threshold for damage or alterations in the typical players of the mitophagic event, such is the case with Parkin mutations in Parkinson's Disease) that renders it more sensitive to the insult, then ROS generation can be too elevated and widespread for the cell to repopulate the mitochondrial pool. In this case, the insult will normally lead to cell death, typically by apoptosis.”[61.7]

[See: Adipocytes, Adipogenesis, Lipolysis, & Macronutrients: Macronutrients & Mitohormesis]

Muscle Atrophy

Muscle fibers are capable of atrophying due to many reasons, the most common is Protein Breakdown, when Actin and Myosin are broken down into peptides and amino acids. Muscle atrophy is often visualized as a balloon (myotube) deflating, but it is far more serious, as tissue is actually lost to degradation.

There are many different Muscle Atrophy Factors / Proteins, the first type become activated during unloading-detraining, such as FOXO3, MuRf1, MAFbx, Atrogin-1, & Myostatin. FOXO3 stimulates MuRf1 / MAFbx which mark muscle for breakdown by adding Ubiquitin to them thereby signaling them for degradation through Proteasome activation, which is internal machinery within muscle tissue that activates proteolysis.
The second type of Muscle Atrophy Factors only promote muscle atrophy when chronically stimulated, such as Cortisol, IL-6, TNF-a, & IL-1B.
The Myonuclei of the secondary myotubes that atrophy merge to the adjacent or subjacent myotubes, thus maintaining a “Muscle Memory” of hypertrophy to allow the body to recover the lost tissue upon reloading or refeeding.



It is a common mistake that many strength and power athletes make to attempt to maintain the highest levels of muscle hypertrophy and strength conditioning without providing the body adequate time to engage the essential process of autophagy which often parallels proteolysis and muscle atrophy. The body functions best by cycling between phases of anabolism and catabolism, and taking into account the existence of myonuclei, an intelligent and physically capable individual should not fear experimentation with short duration fasting, or detraining, whereas in the case of individuals who have not accrued a sufficiently high number of myonuclei (those who have been and continue to be physically inactive), proteolysis and detraining pose a far greater risk towards the development of an often fatal and progressive sarcopenia.

Put succinctly:

"<>Muscle atrophy occurs as the result of changes in the balance between anabolic and catabolic processes, with the result being a loss of muscle mass when protein breakdown exceeds protein synthesis. At the end of the 20th century, a primary driver of muscle atrophy, under most conditions, was thought to be an increase in protein degradation. In 1969, Goldberg demonstrated that an increase in protein degradation contributed to the loss of muscle mass and myofibrillar proteins following denervation and glucocorticoid treatment. Subsequently, it was shown that increases in proteolysis occur in a variety of muscle-wasting conditions, including sepsis, cancer, burns, diabetes, and starvation, and that the primary pathway responsible for the increase in muscle proteolysis under these catabolic conditions was the ATP-dependent, ubiquitin-proteasome pathway. What remained a mystery, however, were the molecular mediators of protein degradation and the atrophy process. Moreover, it was unknown whether muscle atrophy, caused by different stressors, was regulated by a common signaling pathway."[62]

[A] Cortisol, a potent atrophy factor, which reduces protein synthesis, causes fast twitch fiber atrophy in the deeper regions of muscle tissue.
[See: Anti-Inflammation Supplementation: L-Ornithine, Rooibos Tea]

"<>Exercise has been shown to be effective in preventing glucocorticoid-induced atrophy in muscles containing high proportions of type II or fast-twitch fibers. This investigation was undertaken to further evaluate this response in type IIa and IIb fibers, determined by histochemical staining for myofibrillar adenosinetriphosphatase with alkaline and acid preincubation. Steroid [cortisol acetate (CA), 100 mg/kg body wt] and exercise (running 90 min/day, 29 m/min) treatments were initiated simultaneously for 11 consecutive days in female rats. Fiber distribution and area measurements were performed in a deep and superficial region of plantaris muscle. <>The exercise regimen spared approximately 40% of the CA-induced plantaris muscle atrophy. In the deep region, the fiber population, which contained approximately 13% type I (slow-twitch), 24% type IIa, and 63% IIb fibers, was not affected by either treatment. In the superficial section, which consisted solely of type II fibers, the proportion of type IIa fibers was higher (27 vs. 9%, P less than 0.01) in the steroid- than in the vehicle-treated groups. Within each region, type IIa fibers were less susceptible to atrophy than type IIb fibers, and within each fiber type, the deep region had less atrophy than the superficial region. Type I fibers were unchanged by steroid treatment. For type IIa fibers, exercise prevented 100% of the atrophy in the deep region and 50% in the superficial region. For type IIb fibers, the activity spared 67 and 40% of the atrophy in these same regions, respectively.
<>These results show that glucocorticoids are capable of changing the myosin phenotype.[62.1]

[B] 24h of physical inactivity (not regeneration) is enough time to begin the process of muscle atrophy. This does not mean detraining is useless, it means that the process of atrophy begins extremely early, and muscles must be trained at the very least twice a

week to maintain optimal size and function. But this does not equate to two highly destructive workouts in a week, I am certain that even extended aerobic exercise with variegated exercise form is enough to fend off muscle atrophy, but this would not be ideal for maintaining muscle conditioning, or the highest levels of muscle hypertrophy.

"<>In 2001, two reports that identified two novel E3 ubiquitin ligases as key regulators of muscle atrophy were published. In Bodine et al., a differential display approach was used to identify MuRF1 and MAFbx as genes that are similarly altered under disparate atrophy conditions, including immobilization, denervation, hindlimb unloading, dexamethasone treatment, and interleukin-1-induced cachexia. The approach taken was designed to identify a common trigger for atrophy and measured differentially expressed genes in the rat medial gastrocnemius after 3 days of ankle immobilization and then determined whether a subset of genes was universally modified in other types of muscle atrophy. This approach revealed two genes whose expression was relatively low in resting skeletal muscle but increased significantly within 24 h of inactivity or decreased loading."[63]

[B2] Muscle Atrophy Factors do not associate with aging, leading me to believe that cellular senescence, muscle disuse, hypoproteinemia, NSAID's, toxic pharmaceutic drugs, excess Palmitic acid consumption, and Chronic Alcohol-use are the primary causes of muscle loss in the elderly. Although clearly, the greatest enemy to muscle function is disuse, and this is the primary causer of pathological forms of muscle atrophy in the elderly.

"<>Muscle atrophy in many conditions share a common mechanism in the upregulation of the muscle-specific ubiquitin E3-ligases atrophy gene-1/muscle atrophy F-box (Atrogin-1/MAFbx) and muscle ring-finger protein 1 (MuRF1). E3-ligases are part of the ubiquitin proteasome pathway utilized for protein degradation during muscle atrophy. In this study, we provide new data to show that this is not the case in age-related loss of muscle mass (sarcopenia). On the contrary, Atrogin-1/MAFbx and MuRF1 are downregulated in skeletal muscle of 30-month-old rats, and our results suggest that AKT (protein kinase B)-mediated inactivation of forkhead box O 4 (FOXO4) underlies this suppression. The data also suggest that activation of AKT is mediated through the insulin-like growth factor-1 (IGF-1) receptor, signaling via ShcA-Grb2-GAB. Using dietary restriction, we find that it impedes sarcopenia as well as the effects of aging on AKT phosphorylation, FOXO4 phosphorylation, and Atrogin-1/MAFbx and MuRF1 transcript regulation. We conclude that sarcopenia is mechanistically different from acute atrophies induced by disuse, disease, and denervation."[64]

[See: Anti-Aging / Life Extension: Acrolein]

Nociception

Nociception describes the process of pain generation, when tissue injury has occurred or is actively occurring, nociceptors activate and send complex signals originating from afferent nerve fibers to our spine, where they reach certain parts of our cerebral cortex to activate certain subsets of neurons. Neuropathic pain often describes chronic pain, where spinal nerves become overactive, leading to hypersensitivity, or when deafferentation occurs through physical injury such as amputation (when nerves are deprived of sensory input) . Nociceptive pain generally refers to acute physical injury, such as burns, cuts, or musculoskeletal injuries.

Most of us may wonder, why does pain—hurt? Why is pain unpleasant (for most sane individuals)? We know for certain that the primordial experience of pain originated due to physical injury, and not psychological, and therefore a simplistic answer is that "pain" is just a survival signal created to facilitate an *escape-from-a-stimuli* response, but analyzing this issue further I have discovered that peripheral nerve injuries result in GABAergic cell death in the spinal cord, which increases the risk of developing allodynia (chronic pain) through causing an adaptive hypersensitivity to further nerve stimulation[A].

Quite amazingly, GABAergic neurons are also lost in the brain following chronic pain exposure[A]-[B].

If the experience of chronic physical pain causes a permanent loss in inhibitory neurons in the thalamus which controls sensory filtering (the facilitation of attention)[B2], and has been shown to enhance LTP in other brain regions such as the Insular Cortex[C] which enhances recognition memory[C2], and finally has been shown to increase AMPA receptor activity in the Nucleus Accumbens[D] which enhances spatial working memory[D2], then we can logically suggest that one of the adaptive effects of chronic pain is to enhance brain LTP, for with enhanced LTP comes a greater ability to avoid future "*noxious stimuli*", i.e. painful stimuli, through enhanced memory formation, thereby allowing for the development aversive behaviors, which ensure future survival. Also, if pain causes neuronal excitotoxicity, then we have another reason to explain the great feeling of "unpleasure" (Read: Freud's Project) that reactionarily occurs during the experience of pain.

Of note, owing to the research below, it is clear that pain is unpleasant for an additional reason; The enhanced consciousness that accompanies chronic pain results in heightened cortical excitation (anxiety-intelligence). NMDA antagonists such as Ketamine, or other chemicals that inhibit LTP (reduce consciousness) are well documented to have strong antinociceptive effects in human subjects. It is well understood that the pain a mother experiences during the process of giving birth strengthens her emotional bonding to her child, pain is therefore to be considered a psycho-evolutionary adaptative reactionary process for the promotion of learning and emotional connection, which evolved through simplistic survivalism signals.

[A] A study by Thang M. Khuong, Qiao-Ping Wang, John Manion, Lisa J. Oyston, Man-Tat Lau, Harry Towler, Yong Qi Lin, and G. Gregory Neely.

"<>In this study, we show that D. melanogaster can enter a neuropathic pain–like state after injury. By combining behavioral assessment of neuropathic allodynia with genetic and electrophysiological approaches, we performed a systematic molecular dissection of this phenomenon from [the] first principles. We identified a novel neuropathic cascade emanating from the injured peripheral neuron and triggering nAChRα1/twist/caspase-mediated excitotoxic death of central GABAergic inhibitory neurons, culminating in neuropathic allodynia. Together, these data highlight a previously unknown neuropathic injury response program that promotes heightened sensory vigilance and an augmented escape response changes that may help promote survival in dangerous environments.
<>We found that damaging the fly leg triggered heat allodynia, and this occurred through a neuropathic mechanism. After the initial damage, the remaining sensory neurons in the leg exhibited peripheral degeneration as allodynia developed, and in human pain patients, peripheral neuropathy is a common cause of neuropathic pain. While our study here is the first description of long-lasting chronic pain in the fly, there are numerous studies describing models of peripheral neuropathy in larvae or adult flies.
<>While long-lasting chronic pain is not possible to evaluate in Drosophila larval, adult flies also exhibit a marked impairment of motor function in response to the chemotherapeutic cisplatin. This response is likely a result of peripheral neuropathy and may involve pain; however, because of the motor dysfunction observed directly, evaluating pain in this system is difficult. Together, there are now multiple available systems to dissect peripheral neuropathies and neuropathic pain in the fly, and Drosophila genetics coupled with mammalian validation will be a powerful system to investigate the molecular mechanisms leading to both painful and painless neuropathies.
<>It is not completely clear why chronic pain develops after injury. In rodents, pain sensitivities are modulated by GABAergic central inhibition in the spinal cord, and a loss of GABA-dependent inhibitory postsynaptic potential (PSP) can be observed after some forms of nerve injury. This is accompanied by a decrease in GABA release and reduced expression of the GABA synthesizing enzymes. Loss of central GABA has also been observed in humans suffering from chronic neuropathic pain. Moreover, genetic ablation of spinal inhibitory populations is sufficient to cause allodynia in mice. Transplanting GABAergic interneurons into the spinal cord of mice suffering from neuropathic pain can reverse mechanical allodynia. <>Mechanistically, the reduction in spinal GABA may be linked to GABAergic Ca^{2+} influx, reactive oxygen species, and apoptosis of GABAergic interneurons. While systemic antioxidant treatment or intrathecal delivery of a specific caspase inhibitor can prevent GABAergic cell death and attenuate neuropathic pain behavior, definitive genetic proof that death of GABAergic interneurons cause neuropathic sensitization was, until now, lacking.

<>In our system, we observed GABAergic apoptosis after injury, and this led to changes in the nociceptive escape circuit physiology and behavioral sensitization to innocuous temperature, all of which are hallmarks of human neuropathic pain. Through precise genetic manipulation, we could inhibit caspase-dependent cell death specifically in GABAergic interneurons in the VNC, and this completely blocked development of the neuropathic pain–like state in flies.
<>Of note, while we assume that contralateral hypersensitization was caused via excitotoxic acetylcholine release from the injured leg, it is also possible that injury causes a compensatory increase in activity of the contralateral leg, and this increased contralateral movement then drives central GABAergic cell death. Regardless, dysregulation of central GABA tone appears to be a core conserved mechanism critical for neuropathic pain disease across diverse species."
"<>In many ways, chronic pain states exhibit similarities with experience-driven learning and memory. For example, repeated stimulation of primary sensory afferents is sufficient to induce a state of postsynaptic long-term potentiation in the mammalian spinal cord, and the capacity for a similar nociceptive sensitization has been reported in various invertebrate systems. Peripheral stimulation and the resulting central synaptic changes are key molecular events leading to nociceptive sensitization during some forms of chronic pain.
<>In the adult fly, we also observed experience-driven plasticity of nociception circuitry, including an overall increase in the velocity of impulse transmission from sensory neuron to escape muscles, increased persistence of nociceptive response after stimulation, and increased probability of response. These data are compatible with synaptic reinforcement within the dedicated nociception circuit, or alternatively after injury, nociceptive responses could be rerouted through an alternate escape circuit with different response properties. Whether the observed change in escape circuit properties involve synaptic plasticity similar to spinal long-term potentiation in mammals remains to be addressed; however, our genetic evidence places GABAergic cell death as a critical upstream event leading to global changes both in circuitry and neuropathic sensitization in the fly."[64.A] [Truncated]

[B] "<>Human brain imaging has revealed that acute pain results from activation of a network of brain regions, including the somatosensory, insular, prefrontal, and cingulate cortices. In contrast, many investigations report little or no alteration in brain activity associated with chronic pain, particularly neuropathic pain. It has been hypothesized that neuropathic pain results from misinterpretation of thalamocortical activity, and recent evidence has revealed altered thalamocortical rhythm in individuals with neuropathic pain.
<>Indeed, it was suggested nearly four decades ago that neuropathic pain may be maintained by a discrete central generator, possibly within the thalamus. In this investigation, we used multiple brain imaging techniques to explore central changes in

subjects with neuropathic pain of the trigeminal nerve resulting in most cases (20 of 23) from a surgical event.
<>Individuals with chronic neuropathic pain displayed significant somatosensory thalamus volume loss (voxel-based morphometry) which was associated with decreased thalamic reticular nucleus and primary somatosensory cortex activity (quantitative arterial spin labeling).
<>Furthermore, thalamic inhibitory neurotransmitter content was significantly reduced (magnetic resonance spectroscopy), which was significantly correlated to the degree of functional connectivity between the somatosensory thalamus and cortical regions including the primary and secondary somatosensory cortices, anterior insula, and cerebellar cortex. These data suggest that chronic neuropathic pain is associated with altered thalamic anatomy and activity, which may result in disturbed thalamocortical circuits. This disturbed thalamocortical activity may result in the constant perception of pain."[64.B]

[B2] "<>The thalamic reticular nucleus (TRN) plays key roles in sensory processing, arousal and cognition. It consists of a shell of GABAergic neurons, receives inputs from cortical and subcortical regions, and provides the major inhibition to thalamocortical (TC) neurons. During quiescence, the TRN participates in sleep rhythm generation, sleep stability and memory consolidation, while in active states, TRN neurons contribute to sensory filtering underlying attention."[64.C]

[C] "<>Animal and human studies have consistently demonstrated that cortical regions are important for pain perception and pain-related emotional changes. Studies of the anterior cingulate cortex (ACC) have shown that adult cortical synapses can be modified after peripheral injuries, and long-term changes at synaptic level may contribute to long-lasting suffering in patients. It also explains why chronic pain is resistant to conventional analgesics that act by inhibiting synaptic transmission. Insular cortex (IC), another critical cortical area, is found to be highly plastic and can undergo long-term potentiation (LTP) after injury. Inhibiting IC LTP reduces behavioral sensitization caused by injury. LTP of glutamatergic transmission in pain related cortical areas serves as a key mechanism for chronic pain."[64.D]

[C2] "<>For a long time, the insular cortex (IC) has been related with taste physiology and taste memory processes in animal studies. Recently, the role of the IC has been highlighted by findings involving the IC in non-taste memory formation in both human and animal studies. Recognition memory is based on the ability to assess the familiarity of a previously encountered stimulus, and it is considered a form of declarative memory. In this work, I am proposing that the IC and its related circuitry are highly involved in the conversion of novel to familiar stimulus for both object and taste recognition memory. In addition, I will review some of the molecular mechanisms involved in the modification of

novelty to familiarity memory processes, including the role of epigenetic mechanisms on the consolidation of recognition memory within the IC. In the second part of the paper, I will review some of the possible mechanisms to transform a novel taste into a familiar aversive taste by a functional interaction between the IC and the amygdala. In summary, the IC is an important area that will open a new avenue for the study of the mechanisms involved in the neurobiology of learning and memory in the near future."[64.E]

[D] "<>Background: A variety of pain conditions have been found to be associated with depressed mood in clinical studies. Depression-like behaviors have also been described in animal models of persistent or chronic pain. In rodent chronic neuropathic pain models, elevated levels of GluA1 subunits of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the nucleus accumbens (NAc) have been found to inhibit depressive symptoms. However, the effect of reversible post-surgical pain or inflammatory pain on affective behaviors such as depression has not been well characterized in animal models. Neither is it known what time frame is required to elicit AMPA receptor subunit changes in the NAc in various pain conditions.
<>Results: In this study, we compared behavioral and biochemical changes in three pain models: the paw incision (PI) model for post-incisional pain, the Complete Freund's Adjuvant (CFA) model for persistent but reversible inflammatory pain, and the spared nerve injury (SNI) model for chronic postoperative neuropathic pain. In all three models, rats developed depressive symptoms that were concurrent with the presentation of sensory allodynia. GluA1 levels at the synapses of the NAc, however, differed in these three models. The level of GluA1 subunits of AMPA-type receptors at NAc synapses was not altered in the PI model. GluA1 levels were elevated in the CFA model after a period (7 d) of persistent pain, leading to the formation of GluA2-lacking AMPA receptors. As pain symptoms began to resolve, however, GluA1 levels returned to baseline. Meanwhile, in the SNI model, in which pain persisted beyond 14 days, GluA1 levels began to rise after pain became persistent and remained elevated. In addition, we found that blocking GluA2-lacking AMPA receptors in the NAc further decreased the depressive symptoms only in persistent pain models.
<>Conclusion: Our study shows that while both short-term and persistent pain can trigger depression-like behaviors, GluA1 upregulation in the NAc likely represents a unique adaptive response to minimize depressive symptoms in persistent pain states."[64.F]

[D2] "<>Genetically modified mice, lacking the GluA1 AMPA receptor subunit, are impaired on spatial working memory tasks, but display normal acquisition of spatial reference memory tasks. One explanation for this dissociation is that working memory, win-shift performance engages a GluA1-dependent, non-associative, short-term memory process through which animals choose relatively novel arms in preference to relatively familiar options.

<>In contrast, spatial reference memory, as exemplified by the Morris water maze task, reflects a GluA1-independent, associative, long-term memory mechanism. These results can be accommodated by Wagner's dual-process model of memory in which short and long-term memory mechanisms exist in parallel and, under certain circumstances, compete with each other. According to our analysis, GluA1−/− mice lack short-term memory for recently experienced spatial stimuli. One consequence of this impairment is that these stimuli should remain surprising and thus be better able to form long-term associative representations.
<>Consistent with this hypothesis, we have recently shown that long-term spatial memory for recently visited locations is enhanced in GluA1−/− mice, despite impairments in hippocampal synaptic plasticity. Taken together, these results support a role for GluA1-containing AMPA receptors in short-term habituation, and in modulating the intensity or perceived salience of stimuli."[64.G]

Primary Opioid Receptors & Affect

MOR receptors (μ-opioid receptors)

MOR receptor agonists are the primary analgesics used in medicine, and drugs with agonism for the MOR receptors exert powerful euphoric effects, enhance sociality, and reduce anxiety.

"<>Opioid receptors are expressed in pain-modulating descending pathways, which include the medulla locus coeruleus, and periaqueductal gray area. They are also expressed in limbic, midbrain, and cortical structures. The activation of opioid receptors at these locations directly inhibit neurons, which in turn inhibit spinal cord pain transmission. The process by which these receptors engage in disinhibition is mostly understood with respect to analgesia; however research is still active in this area because investigators continue to unravel novel modulatory mechanisms in these opioid circuits."[64.H]

[A] In a theoretical but highly plausible study, pain tolerance was tested through an isotension squat movement, likely to lactic acid failure, in relation to suspected brain MOR opioid receptor activity. It was found that individuals with greater pain tolerance have a larger social network size, and this is thought to relate to decreased opioidergic signaling in the brains of individuals with lower pain thresholds and decreased social network sizes. Why then are low dose opioids not prescribed for antisocial personality disorders?

"<>Personal social network size exhibits considerable variation in the human population and is associated with both physical and mental health status. Much of this inter-individual variation in human sociality remains unexplained from a biological perspective. According to the brain opioid theory of social attachment, binding of the neuropeptide β-endorphin to μ-opioid receptors in the central nervous system (CNS) is a key neurochemical mechanism involved in social bonding, particularly amongst primates. <>We hypothesize that a positive association exists between activity of the μ-opioid system and the number of social relationships that an individual maintains. Given the powerful analgesic properties of β-endorphin, we tested this hypothesis using pain tolerance as an assay for activation of the endogenous μ-opioid system.
<>We show that a simple measure of pain tolerance correlates with social network size in humans. Our results are in line with previous studies suggesting that μ-opioid receptor signaling has been elaborated beyond its basic function of pain modulation to play an important role in managing our social encounters. The neuroplasticity of the μ-opioid system is of future research interest, especially with respect to psychiatric disorders associated with symptoms of social withdrawal and anhedonia, both of which are strongly modulated by endogenous opioids."
"<>Our results show that pain tolerance positively predicts social network size. This therefore supports our hypothesis that variation in the μ-opioid system underlies individual differences in sociality. These results are consistent with a recent PET imaging experiment demonstrating a correlation between μ-opioid receptor availability and attachment style, such that individuals showing greater avoidance of social attachment exhibit lower receptor densities."[64.I]
[B] Music-making stimulates the release of endorphins, which activate the opioid receptors.

"<>It is well known that music arouses emotional responses. In addition, it has long been thought to play an important role in creating a sense of community, especially in small scale societies. One mechanism by which it might do this is through the endorphin system, and there is evidence to support this claim. Using pain threshold as an assay for CNS endorphin release, we ask whether it is the auditory perception of music that triggers this effect or the active performance of music.
<>We show that singing, dancing and drumming all trigger endorphin release (indexed by an increase in post-activity pain tolerance) in contexts where merely listening to music and low energy musical activities do not. We also confirm that music performance results in elevated positive (but not negative) affect. We conclude that it is the active performance of music that generates the endorphin high, not the music itself. We discuss the implications of this in the context of community bonding mechanisms that commonly involve dance and music-making."[64.J]

[C] Laugher in a social setting increases opioid signaling in multiple brain regions, and higher level resting opioid receptor function increases the propensity of individuals to engage in laugher.

"<>The size of human social networks significantly exceeds the network that can be maintained by social grooming or touching in other primates. It has been proposed that endogenous opioid release after social laughter would provide a neurochemical pathway supporting long-term relationships in humans (Dunbar, 2012), yet this hypothesis currently lacks direct neurophysiological support. We used PET and the μ-opioid-receptor (MOR)-specific ligand [11C]carfentanil to quantify laughter-induced endogenous opioid release in 12 healthy males.
<>Before the social laughter scan, the subjects watched laughter-inducing comedy clips with their close friends for 30 min. Before the baseline scan, subjects spent 30 min alone in the testing room. Social laughter increased pleasurable sensations and triggered endogenous opioid release in thalamus, caudate nucleus, and anterior insula. In addition, baseline MOR availability in the cingulate and orbitofrontal cortices was associated with the rate of social laughter.
<>In a behavioral control experiment, pain threshold—a proxy of endogenous opioidergic activation—was elevated significantly more in both male and female volunteers after watching laughter-inducing comedy versus non-laughter-inducing drama in groups. Modulation of opioidergic activity by social laughter may be an important neurochemical pathway that supports the formation, reinforcement, and maintenance of human social bonds.
<>SIGNIFICANCE STATEMENT: Social contacts are vital to humans. The size of human social networks significantly exceeds the network that can be maintained by social grooming in other primates. Here, we used PET to show that endogenous opioid release after social laughter may provide a neurochemical mechanism supporting long-term relationships in humans. Participants were scanned twice: after a 30 min social laughter session and after spending 30 min alone in the testing room (baseline). Endogenous opioid release was stronger after laughter versus the baseline scan. Opioid receptor density in the frontal cortex predicted social laughter rates. Modulation of the opioidergic activity by social laughter may be an important neurochemical mechanism reinforcing and maintaining social bonds between humans."[64.K]

[D] Chronic pain results in a decrease in MOR opioid receptor function. Thus, prescription opioid use in individuals who have suffered a nerve injury is not only morally righteous, but scientifically justifiable.

"<>The opioid system plays a critical role in both the experience and management of pain. Although acute activation of the opioid system can lead to pain relief, the effects of chronic pain on the opioid system remain opaque. Cross-sectional positron emission

tomography (PET) studies show reduced availability of brain opioid receptors in patients with chronic pain but are unable to (1) determine whether these changes are due to the chronic pain itself or due to preexisting or medication-induced differences in the endogenous opioid system, and (2) identify the neurobiological substrate of reduced opioid receptor availability. We investigated these possibilities using a well-controlled longitudinal study design in rat.
<>Using [F]-FDPN-PET in either sham rats (n = 17) or spared nerve injury rats (n = 17), we confirmed reduced opioid receptor availability in the insula, caudate-putamen, and motor cortex of nerve injured rats 3 months after surgery, indicating that painful neuropathy altered the endogenous opioid system. Immunohistochemistry showed reduced expression of the mu-opioid receptor, MOR1, in the caudate-putamen and insula. Neither the opioid peptide enkephalin nor the neuronal marker NeuN differed between groups. In nerve-injured animals, sucrose preference, a measure of anhedonia/depression-like behavior, positively correlated with PET opioid receptor availability and MOR1-immunoreactivity in the caudate-putamen.
<>These findings provide new evidence that the altered supraspinal opioid receptor availability observed in human patients with chronic pain may be a direct result of chronic pain. Moreover, reduced opioid receptor availability seems to reflect decreased receptor expression, which may contribute to pain-induced depression."[64.L]

KOR receptors (Kappa opioid receptors)

The KOR opioid receptors exert powerful depressogenic effects, possibly as an evolutionary adaptation[D].

[A] KOR receptors, which are activated by way of the neuropeptide Dynophorin, are necessary for the development of stress-induced dysphoria, and aversive behavior.

"<>Stress is a complex human experience having both positive and negative motivational properties. When chronic and uncontrollable, the adverse effects of stress on human health are considerable and yet poorly understood. Here, we report that the dysphoric properties of chronic stress are encoded by the endogenous opioid peptide dynorphin acting on specific stress-related neuronal circuits.
<>Using different forms of stress presumed to evoke dysphoria in mice, we found that repeated forced swim and inescapable footshock both produced aversive behaviors that were blocked by a κ-opioid receptor (KOR) antagonist and absent in mice lacking dynorphin. Injection of corticotropin-releasing factor (CRF) or urocortin III, key mediators of the stress response, produced place aversion that was also blocked by dynorphin gene deletion or KOR antagonism. CRF-induced place aversion was blocked by the CRF2 receptor antagonist antisauvigine-30, but not by the CRF1 receptor antagonist antalarmin.

<>In contrast, place aversion induced by the KOR agonist U50,488 was not blocked by antisauvigine-30. These results suggest that the aversive effects of stress were mediated by CRF2 receptor stimulation of dynorphin release and subsequent KOR activation. Using a phospho-selective antibody directed against the activated KOR to image sites of dynorphin action in the brain, we found that stress and CRF each caused dynorphin-dependent KOR activation in the basolateral amygdala, nucleus accumbens, dorsal raphe, and hippocampus.
<>The convergence of stress-induced aversive inputs on the dynorphin system was unexpected, implicates dynorphin as a key mediator of dysphoria, and emphasizes κ-receptor antagonists as promising therapeutics."[64.M]

[B] The KOR receptors likely cause derangements in behavior through reducing dopamine availability in certain discrete brain regions[B1] and activating the NR2B receptors[B2]. [See: Agmatine [324.A]]

[B1] "<>The nucleus accumbens (NAc) core is involved in regulating stress and shaping reward seeking behaviours. Multiple neuromodulators, including dynorphin/kappa opioid receptor (KOR) and dopamine systems, converge in this area to influence behavioural outcomes.
<>KOR activation acutely inhibits dopamine release and chronically depresses overall dopamine transmission. Recently, studies in the NAc shell have revealed that the impact of KOR activation on behaviour is regionally specific, and these rostro-caudal differences are likely driven by greater control of KORs over dopamine inhibition in the caudal compared with rostral subregion. Given the importance of NAc core, particularly the interaction between KORs and dopamine in regulating reward seeking behaviours, we examined the impact of KOR activation on dopamine release and uptake along the rostro-caudal axis in the NAc core of male and female mice.
<>Using ex vivo fast scan cyclic voltammetry, we observed that KOR mediated inhibition of dopamine release was significantly greater in caudal compared with rostral NAc core with no significant sex differences observed. These data suggest that KORs regulate dopamine release differentially along the rostro-caudal axis, providing a new axis on which to examine the process by which the KOR/dopamine system controls reward encoding."[64.N]

[B2] "<>Psychotomimetic and prodepressive effect by kappa opioid receptor (KOR) activation in rodents and human is widely known. Significantly, recent clinical investigations demonstrated the salutary effects of KOR antagonists in patients with treatment resistant depression, indicating essential role of KOR signaling in refractory depression. This study was undertaken to reveal the molecular determinant of KOR mediated depression and antidepressant response of KOR antagonist.

<>We observed that chronic KOR activation by U50488, a selective KOR agonist, significantly increased depression like symptoms (behavioral despair, anhedonia, and sociability) in C57BL/6J mice, which were blocked by KOR antagonist norBNI and antidepressant imipramine, but not by fluoxetine or citalopram.
<>Further, chronic KOR activation increased phosphorylation of NR2B subunit of NMDA at tyrosine 1472 (pNR2B NMDA) in the hippocampus, but not in the cortex. Similar to behavioral effects norBNI and imipramine, but not SSRIs, blocked NR2B phosphorylation. Moreover, KOR induced depression like behaviors were reversed by NR2B selective inhibitor Ro 25-6981.
<>Mechanistic studies in primary cultured neurons and brain tissues using genetic and pharmacological approaches revealed that stimulation of KOR modulates several molecular correlates of depression. Thus, these findings elucidate molecular mechanism of KOR signaling in treatment resistant depression like behaviors in mice."[64.O]

[C] The KOR receptors inhibit LTP, potentially explained by me as an evolutionary psychological survival mechanism to reduce cognition during high stress scenarios.

"NMDA receptor-mediated long-term potentiation (LTP) of dentate granule cell responses to perforant path stimulation was inhibited by the kappa 1 opioid receptor agonist U69,593. This inhibition was reversed stereospecifically by naloxone and blocked by the selective kappa 1 antagonist norbinaltorphimine (NBNI). NBNI, by itself, had no effect on LTP induced by threshold stimulation but significantly enhanced LTP from more prolonged stimulation. This effect of NBNI suggests that endogenous opioids can regulate LTP in the dentate gyrus. In support of this hypothesis, stimulation of dynorphin-containing fibers also blocked LTP production in an NBNI-sensitive manner. Finally, dynorphin-mediated inhibition of LTP acts primarily on mechanisms of induction rather than maintenance or expression, since dynorphin released immediately before, but not immediately after, perforant path stimulation blocked LTP. Thus, exogenous and endogenous kappa opioids can inhibit induction of long-term potentiation at the perforant path-granule cell synapse and may therefore regulate plastic changes in synaptic transmission in a brain region thought to play an important role in processes of both learning and memory and epileptogenesis."[64.P]

[D] Here are correlated and highly interesting theories explaining the evolutionary advantage and purpose of depression called the **Infection-defense hypothesis[1]**, & **Pathogen-Host Defense hypothesis[2]**, both of which, to my limited understanding, posit that the cause of depression is either weakened cellular immunity due to environmental toxins, genetic conditions, infection, or most frequently systemic inflammation (Inflammatory Factors), thereby promoting depression i.e. antisocial behaviors, and a "low energy state", which mitigates our risk for further

immunocompromisation, possible infection, and eventual death, conferring an evolutionary advantage towards survival.

[1] "<>Recent discoveries relating depression to inflammation and immune function may help to solve an important evolutionary puzzle: If depression carries with it so many negative consequences, including notable costs to survival and reproduction, then why is it common and heritable? What countervailing force or compensatory advantage has allowed susceptibility genes for depression to persist in the population at such high rates? A priori, compensatory advantages in combating infection are a promising candidate, given that infection has been the major cause of mortality throughout human history. Emerging evidence on deeply rooted bidirectional pathways of communication between the nervous and immune systems further supports this notion.
<>Here we present an updated review of the "infection-defense hypothesis" of depression, which proposes that moods—with their ability to orchestrate a wide array of physical and behavioral responses—have played an adaptive role throughout human history by helping individuals fight existing infections, as well as helping both individuals and their kin avoid new ones. We discuss new evidence that supports several key predictions derived from the hypothesis, and compare it with other major evolutionary theories of depression. Specifically, we discuss how the infection-defense hypothesis helps to explain emerging data on psychoimmunological features of depression, as well as depression's associations with a diverse array of conditions and illnesses—including nutritional deficiencies, seasonal changes, hormonal fluctuations, and chronic diseases—that previous evolutionary theories of depression have not accounted for. Finally, we note the potential implications of the hypothesis for the treatment and prevention of depression."
"<>Numerous associations between depression and immune function have been observed in recent years. Early studies investigating immune alterations during depression focused almost exclusively on markers of suppressed cellular immunity—such as decreased lymphocyte proliferation and natural killer (NK) cell activity."
↓ continued
"<>Increased rates of depressive symptoms have been observed following an individual's contracting a number of acute or subacute infections, as well as following chronic infections, and immunization with live virus vaccines."[64.Q] [Truncated]

[2] "<>Given the manifold ways that depression impairs Darwinian fitness, the persistence in the human genome of risk alleles for the disorder remains a much debated mystery. Evolutionary theories that view depressive symptoms as adaptive fail to provide parsimonious explanations for why even mild depressive symptoms impair fitness-relevant social functioning, whereas theories that suggest that depression is maladaptive fail to account for the high prevalence of depression risk alleles in human populations.

These limitations warrant novel explanations for the origin and persistence of depression risk alleles.
<>Accordingly, studies on risk alleles for depression were identified using PubMed and Ovid MEDLINE to examine data supporting the hypothesis that risk alleles for depression originated and have been retained in the human genome because these alleles promote pathogen host defense, which includes an integrated suite of immunological and behavioral responses to infection. Depression risk alleles identified by both candidate gene and genome-wide association study (GWAS) methodologies were found to be regularly associated with immune responses to infection that were likely to enhance survival in the ancestral environment.
<>Moreover, data support the role of specific depressive symptoms in pathogen host defense including hyperthermia, reduced bodily iron stores, conservation/withdrawal behavior, hypervigilance and anorexia. By shifting the adaptive context of depression risk alleles from relations with conspecifics to relations with the microbial world, the Pathogen Host Defense (PATHOS-D) hypothesis provides a novel explanation for how depression can be nonadaptive in the social realm, whereas its risk alleles are nonetheless represented at prevalence rates that bespeak an adaptive function."[64.R]

Antinociception

Reducing pain signaling in our bodies through natural means is possible but rather difficult, considering the complexity of pain, and the different intensities it can take. Regardless, it is highly possible to achieve noticeable pain relief from the use of non-prescription over-the-counter herbal extracts, isolated phytochemicals, or other chemicals.

Pain, quite interestingly, is not only physical, but psychological. Both chronic physical pain and chronic psychological pain associate with reduced opioid receptor activity in the brain. It must therefore be the goal of any physically or mentally injured man or woman to facilitate opioidergic signaling in their brains, to maintain their social relationships, to continue to laugh.

Although THC is a very strong and soon to be commonly suggested and prescribed antinociceptive drug, I will not be including it in this section, due this study, which showed that antinociceptive tolerance develops rapidly to THC use, especially in female mice, likely paralleling the decreased functionality of the CB1 receptors[1].

[1] "<>Rationale: A reduced effect of a given dose of Δ9-tetrahydrocannabinol (THC) emerges with repeated exposure to the drug. This tolerance can vary depending on THC dose, exposure chronicity and the behavioral or physiological measure of interest. A novel THC inhalation system based on e-cigarette technology has been recently shown to produce the hypothermic and antinociceptive effects of THC in rats.

<>Objective: To determine if tolerance to these effects can be produced with repeated vapor inhalation.
Methods: Groups of male and female Wistar rats were exposed to 30 minutes of inhalation of the propylene glycol (PG) vehicle or THC (200 mg/mL in PG) two or three times per day for four days. Rectal temperature changes and nociception were assessed after the first exposure on the first and fourth days of repeated inhalation.
<>Results: Female, but not male, rats developed tolerance to the hypothermic and antinociceptive effects of THC after four days of twice-daily THC vapor inhalation. Thrice daily inhalation for four days resulted in tolerance in both male and female rats. The plasma THC levels reached after a 30 minute inhalation session did not differ between the male and female rats.
Conclusions: Repeated daily THC inhalation induces tolerance in female and male rats, providing further validation of the vapor inhalation method for preclinical studies."[64.S]

Exercise

Exercise, specifically "aerobic fitness" i.e. cardiovascular exercise, is positively associated with opioid neuropeptide (endorphin) release post-exercise. The more athletic you become, the greater the release of exercise-induced opioid neuropeptides will be.

"<>Introduction: Central μ-opioid receptors (MORs) modulate affective responses to physical exercise. Individuals with higher aerobic fitness report greater exercise-induced mood improvements than those with lower fitness, but the link between cardiorespiratory fitness and the MOR system remains unresolved. Here we tested whether maximal oxygen uptake (V̇O2peak) and physical activity level are associated with cerebral MOR availability and whether these phenotypes predict endogenous opioid release after a session of exercise.
<>Methods: We studied 64 healthy lean men who performed a maximal incremental cycling test for V̇O2peak determination, completed a questionnaire assessing moderate-to-vigorous physical activity (MVPA; in minutes per week), and underwent positron emission tomography with [11C]carfentanil, a specific radioligand for MOR. A subset of 24 subjects underwent additional positron emission tomography scan also after a 1-h session of moderate-intensity exercise and 12 of them also after a bout of high-intensity interval training.
<>Results: Higher self-reported MVPA level predicted greater opioid release after high-intensity interval training, and both V̇O2peak and MVPA level were associated with a larger decrease in cerebral MOR binding after aerobic exercise in the ventral striatum, orbitofrontal cortex, and insula. That is, more trained individuals showed greater opioid release acutely after exercise in brain regions especially relevant for reward and cognitive processing. Fitness was not associated with MOR availability.

<>Conclusions: We conclude that regular exercise training and higher aerobic fitness may induce neuroadaptation within the MOR system, which might contribute to improved emotional and behavioral responses associated with long-term exercise."[64.T]

Kratom (Mitragynine)

Kratom contains the opioid receptor agonist alkaloid Mitragynine. Although Mitragynine, the primary chemical component of interest in Kratom has moderate affinity for MOR (μ-opioid) receptor agonism, it also has high agonism on the Kappa opioid receptors, which isn't that great, but upon further research it appears that in lower concentrations Mitragynine is an antagonist of the Kappa opioid receptors[A], possibly explaining the beneficial effects low dosage Mitragynine exerts on cognition[B-B2].

[A] "mitragynine (1) act as a partial agonist at MOR with a maximal efficacy of 34%. However, at KOR and DOR, the functional activity of mitragynine (1) alkaloid converts from partial agonist to antagonist at lower potency. Additionally, the diastereomers of mitragynine (1), speciogynine (2), and speciociliatine (3) showed null measurable agonist activity at all the opioid receptors and only revealed a weak antagonist effect. By comparing mitragynine (1) and speciogynine (2), the ethyl group at position 20 on ring D shows a crucial point as the epimerization of this group is able to switch the agonistic activity to antagonist activity at MOR. The modification of the configuration of the ethyl group also reduced the binding affinity."[64.U]

[B] In comparing the effects of low dose Mitragynine, high dose Mitragynine, THC, or Morphine, low dose Mitragynine was found to enhance reversal learning and therefore is to be considered a nootropic, whereas high dose Mitragynine was found to cause cognitive inflexibility through potentiating CB1 receptor expression in the brain. The high dosage of Mitragynine in this study is likely not corollary to moderate Kratom use, especially Kratom Tea consumption, but high serum levels of Mitragynine will accumulate from prolonged habitual Kratom use, especially if using extracts, owing to its long half-life of 7-39 hours, making it is necessary to *cycle* Kratom use by incorporating a safe withdrawal period of at minimum two weeks every certain number of months, of which I dare not venture to guess, depending on dosages, and frequency of Kratom use.

"<>Kratom is a widely abused plant-based drug preparation with a global interest in recent years, well beyond its native grounds in Southeast Asia. Mitragynine, its major psychoactive constituent is known to exhibit opioid-like behavioral effects with resultant neuroplasticity in the brain reward system. Its chronic administration is associated with cognitive impairments in animal studies. However, the underlying molecular mechanism for such a deficit remains elusive.

<>In this study, the involvement of cannabinoid type-1 (CB1) receptors in cognitive deficits after chronic mitragynine exposures was investigated for 28 days (with incremental dose sensitization from 1 to 25 mg/kg) in adult male Swiss albino mice using the IntelliCage® system.
<>Chronic high-dose mitragynine exposure (5–25 mg/kg, intraperitoneal [i.p.]), but not low-dose exposure (1–4 mg/kg, i.p.), induced hyperlocomotion, potentiated the preference for sucrose reward, increased resistance to punishment, and impaired place learning and its reversal. Comparable deficits were also observed after chronic treatments with Δ-9-tetrahydrocannabinol (THC, 2 mg/kg, i.p.) or morphine (5 mg/kg, subcutaneous).
<>Mitragynine-, morphine-, and THC-induced learning and memory deficits were reversed by co-treatment with the CB1 receptor antagonist, NIDA-41020 (10 mg/kg, i.p.). A significant upregulation of CB1 receptor expression was found in the hippocampal CA1 region and ventral tegmental area after chronic high-dose mitragynine and morphine, whereas a downregulation was observed after chronic THC.
↓ [The cognitive testing used on the mice in this study]
"<>Place learning (Day 17–21): all doors remained closed, but access to water was restricted to one water-rewarded corner (the individual least preferred corner during nose poke adaptation) termed the "correct corner." Three successive nose pokes at the individual correct corner opened the respective door for 5 s. The percentage of visits with nose pokes to the correct corner were determined as an indicator for learning.
<>Reversal learning (Day 22–28): the same procedure as for place learning was followed, but the correct water-rewarded corner was reversed to the diagonal opposite corner. The percentage of visits with nose pokes in the newly placed correct corner was measured as an indicator for reversal learning."
"<>Overall, the percentage of preference for the new correct corner on Day 22 (the first day of reversal learning) was generally lower than that recorded during Day 17 (the first day of learning phase). Significant increase in acquiring the newly placed correct water-reinforced corner was observed in untreated, Tween-20 vehicle, and low-dose mitragynine groups, implying their significant relearning abilities ($p < 0.05$). Consistent with place learning data, all drug-sensitized groups failed to acquire the reversed correct corner (morphine: $p = 0.004$, THC: $p = 0.002$, high-dose mitragynine: $p = 0.02$ vs control).
<>There were no significant differences in reversal learning deficiency observed between high-dose mitragynine-, morphine-, and THC-sensitized groups (high-dose mitragynine: $p = 0.854$ vs morphine; $p = 0.898$ vs THC)."[64.V]

[B2] A relatively simple explanation on Reversal Learning, which I understand as relating to Error-related Negativity i.e. Cognitive Flexibility.

"<>Another conceptualization of reversal learning emphasizes the notion that the difficulty to disengage from ongoing behavior after a contingency shift reflects a compulsive or habitual response tendency. This suggests that the task measures a set of processes related to automatized behavior, which may also be germane to psychiatric disorders, like addiction."[64.W]

The Spine

Because intervertebral disc injury is one of the most common causes of debilitating chronic pain, I am including this short subsection.

The harder we exercise, the more compression forces occur in our spine, resulting in the risk for spinal disc injuries or degeneration, which will cause debilitating pain in later life. It is vital to attempt to *decompress* the spine after every intense workout, through flexibility exercises such as stretching, yoga, & most importantly the use of an at home rehabilitation device called an Inversion Table[1], which is one of the most important investments an athlete can make. There is also the "Reverse Hyper" machine originally invented by Louie Simmons to rehabilitate his broken back that may decompress the spine, but there is no need to purchase this piece of equipment when you can perform reverse hyperextensions practically anywhere for free by leaning off a bench, or by leaning off a bed.

Flexibility, although often discounted, is of supreme importance to maintaining a healthy spine, but good posture is not often spoke of for the prevention of back injuries, one should sit with perfect posture when seated, to ensure even distribution of gravitational forces on their intervertebral discs[2].

Swimming[3] is one spinal decompression method not many people consider, but it is an easy way to take the stress of gravity off your back, figuratively and literally, not to mention performing warmups (biceps curls, triceps extensions, etc.) in a swimming pool by resisting against the natural force of water with a static open or closed hand position is a very fun and intelligent way to train multiple muscle groups through isolation exercise with no equipment when you have a back injury. I am referring to a specific form of water aerobics, or as it should be described *water resistance training*, where your body is submerged up to the neck, not where your muscles go from submerged to above-water, such as traditional swim exercise classes teach, as that is quite ineffective in my estimation at stimulating muscle growth. Water Resistance Training is excellent for warming up our muscles before more strenuous training, specifically the deltoids, pectorals, hamstrings, and lats (torso rotations).

It may be possible that certain TALMs will be able to prevent the degradation spinal discs experience naturally through aging, and the degradation that is accelerated through high load resistance training, but the research on this subject is extremely limited. Regardless, applying a large amount of inhibitory Essential oils to your spine, when you

are injured, will surely reduce the overactivity of your irritated spinal nerves, and may possibly reduce the inflammatory chemical cascade that destroys spinal discs.
[1] "<>Purpose: Backache and sciatica due to protuberant disc disease is a major cause of lost working days and health expenditure. Surgery is a well-established option in the management flowchart. There is no strong evidence proving that traction for sciatica is effective. We report a pilot prospective randomized controlled trial comparing inversion traction and physiotherapy with standard physiotherapy alone in patients awaiting lumbar disc surgery. This study sought to study the feasibility of a randomized controlled trial on the effect of inversion therapy in patients with single level lumbar discogenic disease, who had been listed for surgery.
<>Methods: This was a single centre prospective randomized controlled trial undertaken at the Regional Neurosciences Centre, Newcastle Upon Tyne, UK. It was a prospective randomized controlled trial where patients awaiting surgery for pure lumbar discogenic disease within the ambit of the prestated inclusion/exclusion criteria were allocated to either physiotherapy or physiotherapy and intermittent traction with an inversion device. Post-treatment assessment made by blinded observers at 6 weeks for various outcome measures included the Roland Morris Disability Questionnaire (RMDQ) Score, Short Form 36 (SF 36), Oswestry Disability Index (ODI), Visual Analogue Pain Score (VAS), magnetic resonance imaging (MRI) appearance and the need for surgery. Avoidance of surgery was considered a treatment success.
<>Results: Twenty-six patients were enrolled and 24 were randomized [13 to inversion + physiotherapy and 11 to physiotherapy alone (control)]. Surgery was avoided in 10 patients (76.9%) in the inversion group, whereas it was averted in only two patients (22.2%) in the control group. Cancellation of the proposed operation was a clinical decision based on the same criteria by which the patient was listed for surgery initially. There were no significant differences in the RMDQ, SF 36, ODI, VAS or MRI results between the two groups.
<>Conclusion: Intermittent traction with an inversion device resulted in a significant reduction in the need for surgery. A larger multicentre prospective randomized controlled trial is justified in patients with sciatica due to single level lumbar disc protrusions."[64.X]

[2] "<>Cadaveric lumbar motion segments were creep loaded for 4 hours, and the fluid content of the intervertebral discs was measured and compared with that of unloaded discs. Half of the specimens were wedged to simulate sitting with the lumbar spine flexed, and the other half were wedged to simulate sitting or standing erect. The results showed that "flexed" discs lost more fluid, especially from the nucleus pulposus, than did the "erect" discs. It is concluded that fluid flow in flexed postures can aid the nutrition of the lumbar discs."[64.X2]

[3]

[A] Speedwalking & Running (not regular-speed walking, or sprinting) delays the aging of intervertebral discs.

"<>There is currently no evidence that the intervertebral discs (IVDs) can respond positively to exercise in humans. Some authors have argued that IVD metabolism in humans is too slow to respond anabolically to exercise within the human lifespan. Here we show that chronic running exercise in men and women is associated with better IVD composition (hydration and proteoglycan content) and with IVD hypertrophy.
<>Via quantitative assessment of physical activity, we further find that accelerations at fast walking and slow running (2 m/s), but not high-impact tasks, lower intensity walking or static positions, correlated to positive IVD characteristics.
<>These findings represent the first evidence in humans that exercise can be beneficial for the IVD and provide support for the notion that specific exercise protocols may improve IVD material properties in the spine. We anticipate that our findings will be a starting point to better define exercise protocols and physical activity profiles for IVD anabolism in humans."[64.Y]

[A2] A protocol involving a periodized running volume protocol in mice subjected to toxin-induced intervertebral disc damage (Week 1: 20-Minutes, Week 2: 30-Minutes,

Week 3-8: 40-Minutes) results in noticeable regeneration of the damaged intervertebral disc.

"<>Chronic low back pain accompanied by intervertebral disk degeneration is a common musculoskeletal disorder. Physical exercise, which is clinically recommended by international guidelines, has proven to be effective for degenerative disc disease (DDD) patients. However, the mechanism underlying the analgesic effects of physical exercise on DDD remains largely unclear.
<>The results of the present study showed that mechanical withdrawal thresholds of bilateral hindpaw were significantly decreased beginning on day three after intradiscal complete Freund's adjuvant (CFA) injection and daily running exercise remarkably reduced allodynia in the CFA exercise group beginning at day 28 compared to the spontaneous recovery group (controls). The hindpaw withdrawal thresholds of the exercise group returned nearly to baseline at the end of experiment, but severe pain persisted in the control group. Histological examinations performed on day 70 revealed that running exercise restored the degenerative discs and increased the cell densities of the annulus fibrosus (AF) and nucleus pulposus (NP). <>Furthermore, immunofluorescence labeling revealed significantly higher numbers of 5-bromo-2-deoxyuridine (BrdU)-positive cells in the exercise group on days 28, 42, 56 and 70, which indicated more rapid proliferation compared to the control at the corresponding time points.
<>Taken together, these results suggest that running exercise might alleviate the mechanical allodynia induced by intradiscal CFA injection via disc repair and cell proliferation, which provides new evidence for future clinical use."[64.Z]

[B] Yoga delays intervertebral disc degeneration, although certain yoga poses are associated with vertebral fractures, especially in the elderly see: [64.0].

"<>The objective of the current study was to find out whether yoga practice was beneficial to the spine by comparing degenerative disc disease in the spines of long-time yoga practitioners and non-yoga practicing controls, using an objective measurement tool, magnetic resonance imaging. This matched case-control study comprised 18 yoga instructors with teaching experience of more than 10 years and 18 non-yoga practicing asymptomatic individuals randomly selected from a health checkup database. A validated grading scale was used to grade the condition of cervical and lumbar discs seen in magnetic resonance imaging of the spine, and the resulting data analyzed statistically.
<>The mean number of years of yoga practice for the yoga group was 12.9 ± 7.5. The overall (cervical + lumbar) disc scores of the yoga group were significantly lower

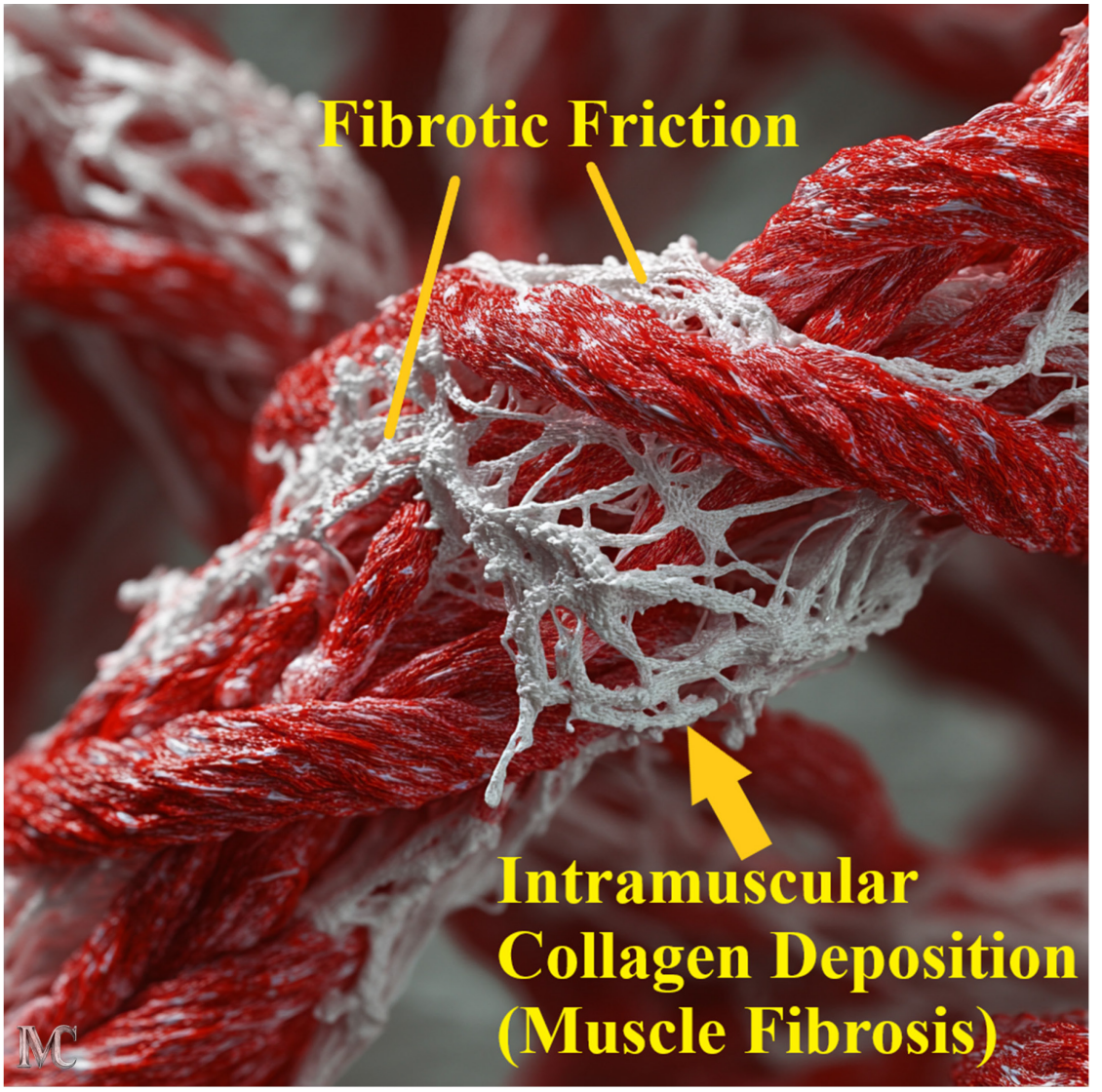
(indicating less degenerative disc disease) than those of the control group ($P < 0.001$). The scores for the cervical vertebral discs of the yoga group were also significantly lower than those of the control group ($P < 0.001$), while the lower scores for the yoga group in the lumbar group approached, but did not reach, statistical significance ($P = 0.055$). <>The scores for individual discs of yoga practitioners showed significantly less degenerative disease at three disc levels, C3/C4, L2/L3 and L3/L4 ($P < 0.05$). Magnetic resonance imaging showed that the group of long-term practitioners of yoga studied had significantly less degenerative disc disease than a matched control group."[64.0.1]

Skeletal Muscle Fibrosis

Muscle Fibrosis plays a large role in muscle loss as we age, due primarily to chronic alcohol use, NSAID's, overtraining, and unfettered inflammatory or unfettered *anti-inflammatory* factors [See: Macrophages: M2 Phenotype].
Muscle fibrosis generally occurs by way of Transforming Growth Factor Beta (TGF-b) which when overexpressed in damaged muscle tissue actively converts regenerating muscle myotubes into fibroblasts (scar tissue: collagen), TGF-b also associates with collagen production in skin and tendons. TGF-b is not necessarily an evil force in our body, even if it is capable of causing such harm, as it plays an integral role in muscle regeneration, maintenance, and skin health.

Intramuscular collagen results in (during contraction) what I refer to as ***Fibrotic Friction***, it impedes muscle contraction and myogenesis, disturbs muscle blood flow, and causes aberrant contraction-induced muscle damage potentially leading to severe forms of muscle tears. The best way to counteract Fibrotic Friction is through frequent painful deep-tissue massage (Shiatsu Massage / A.R.T. Therapy), to restore elasticity and movement to muscle fibers.

It is possible in my view that muscle fibrosis is capable of improving muscle force due to increased muscle fiber tightness, and due to less overall muscle tissue being present, resulting in hyperlocalized mature muscle fibers being able to sequester a greater amount of stem cells, and the greater accretion of myonuclei. Of course, this is only a hypothesis, and the detrimental effects of muscle fibrosis would outweigh any potential benefits.
The amount of muscle fibrosis that develops during overtraining is as of yet unknown, but I am certain after a certain training threshold is surpassed, especially in the presence of an overabundance of M2 (Anti-Inflammatory) Cytokines, or an insufficiency in (Pro-Inflammatory) M1 Cytokines, the process of muscle fibrosis begins. In the myogenic milieu of chronic M1 Cytokines, muscle fibrosis is liable to occur, but only after muscle atrophy has proceeded, it is therefore important to embrace inflammation during times of strenuous training, to ensure efficient muscle and tendon repair following exercise.



[A] TGF-b appears to be vital in maintaining hypertrophied muscle fibers if it is not overexpressed.

“Some studies have suggested that TGF-β is important for myoblast fusion and myotube formation and is essential for proper muscle development. Recently, Gumucio et al. (2015) suggested that TGF-β should not be considered a negative factor for interfering with satellite cell activation. On the contrary, they asserted that TGF-β can actually help optimize satellite cell activation because premature proliferation, differentiation, and fusion of satellite cells interrupt muscle regeneration and may result in the formation of small-sized muscle fibers. In other words, activating satellite cells, before the debris from damaged muscle fibers are completely removed through inflammatory responses, may lead to incomplete structural regeneration. Hence, timely activation of TGF-β and satellite cells is thought to be critical for normal and maximal muscle recovery.”[64.1]

[A2] TGF-b overexpression causes muscle fiber atrophy & fibrosis but is essential for muscle force production.

"Muscle fibers, fibroblasts, and other cells found within the skeletal muscle, when TGF-β level increases, start to extensively synthetize extracellular matrix components. As a result, they contribute to the development of fibrosis followed by muscle fibers atrophy. Even when it does not change muscle mass, consistent with accumulation of ECM, the contractile forces of TGF-β treated muscles are also reduced. Importantly, as TGF-β treatment can directly induce muscle fiber atrophy in the absence of physical injury, reduction in the force generating capacity also affects treated with TGF-β intact muscle (Mendias et al., 2012). Surprisingly, inhibition of TGF-β results in an initial improvement but long-term deficit in the force generation after contraction-induced skeletal muscle injury. It also impairs or at least delays muscle repair".[65]
[B] TGF-b associates with tendon healing 1.

"Flexor tendon healing is complicated by adhesions to the surrounding sheath. Transforming growth factor beta (TGF-beta) is a cytokine with numerous activities related to wound healing. We examined the effects of TGF-beta-1, -2 and -3 on tendon cell proliferation and collagen production. Three separate cell lines--sheath fibroblasts, epitenon and endotenon tenocytes--were isolated from rabbit flexor tendons and cultured separately. Cell culture media was supplemented with 1 or 5 ng/mL of TGF-beta-1, -2, or -3. Cell number and collagen I and III production were measured and compared with unsupplemented control cultures. The addition of TGF-beta to cell culture media resulted in a decrease in cell number in all 3 lines that did not reach statistical significance. There was a significant increase ($p < .05$) in collagen I and III production with the addition of all 3 TGF-beta isoforms. Modulation of TGF-beta production may provide a mechanism to modulate adhesion formation clinically."[66]

[B2] TGF-b associates with tendon healing 2.

"<>Mechanical loading of tissue is known to influence local collagen synthesis, and microdialysis studies indicate that mechanical loading of human tendon during exercise elevates tendinous type I collagen production. Transforming growth factor-β1 (TGF-β1), a potent stimulator of type I collagen synthesis, is released from cultured tendon fibroblasts in response to mechanical loading. Thus TGF-β1 could link mechanical loading and collagen synthesis in tendon tissue in vivo.
<>Tissue levels of TGF-β1 and type I collagen metabolism markers [procollagen I COOH-terminal propeptide (PICP) and COOH-terminal telopeptide of type I collagen (ICTP)] were measured by microdialysis in peritendinous tissue of the Achilles' tendon in six male volunteers before and after treadmill running (1 h, 12 km/h, 3% uphill). In addition, blood levels of TGF-β1, PICP, and ICTP were obtained. PICP levels increased 68 h after exercise ($P < 0.05$). Dialysate levels of TGF-β1 changed from 303 ± 46 pg/ml (at rest) to 423 ± 86 pg/ml 3 h postexercise. This change was nonsignificant, but the

decay of tissue TGF-β1 after catheter insertion was markedly delayed by exercise compared with the decay seen in resting subjects.
<>Plasma concentrations of TGF-β1 rose 30% in response to exercise ($P < 0.05$ vs. pre). Our observations indicate an increased local production of type I collagen in human peritendinous tissue in response to uphill running. Although not conclusive, changes in circulating and local TGF-β1, in response to exercise, suggest a role for TGF-β1 in mechanical regulation of local collagen type I synthesis in tendon-related connective tissue in vivo."[67]

[C] Interestingly, Myostatin inhibition reverses muscle fibrosis. Do understand that this study is elaborating in strong cellular inhibition, not minor cellular inhibition, aside from research chemicals, the odds of you significantly suppressing myostatin expression from supplements islow, but even a minor reduction in this protein will facilitate myogenesis.

"<>Skeletal muscle fibrosis is a defining feature of the muscular dystrophies in which contractile myofibers are replaced by fibroblasts, adipocytes and extracellular matrix. This maladaptive response of muscle to repetitive injury is progressive, self-perpetuating and thus far, has been considered irreversible. We have previously shown that myostatin, a known endogenous modulator of muscle growth, stimulates normal muscle fibroblasts to proliferate.
<>Here, we demonstrate that myostatin also regulates the proliferation of dystrophic muscle fibroblasts and increases resistance of fibroblasts to apoptosis through Smad and MAPK signaling. Inhibition of myostatin signaling pathways with a soluble activin IIB receptor (ActRIIB.Fc) reduces resistance of muscle fibroblasts to apoptosis in vitro. Systemic administration of ActRIIB.Fc in senescent mdx mice, a model of muscular dystrophy, significantly increases the number of muscle fibroblasts undergoing apoptosis. This leads to the reversal of pre-existing muscle fibrosis as determined by histological, biochemical and radiographical criteria.
<>These results demonstrate that skeletal muscle fibrosis can be pharmacologically reversed through induction of fibroblast apoptosis."[67.0]

[See: Anti-Inflammation Cycle Supplementation: Sulforaphane]

[See: Anti-Inflammation Cycle Supplementation: MCT Oil]

Cardiovascular Fibrosis

Aging induces cardiac fibrosis[1], whereas endurance exercise counteracts this pathogenic process[2], and these processes are unrelated to MMP expression, giving you one more reason to engage in chronic cardiovascular exercise.

[1] "<>The aging heart is characterized by morphological and structural changes that lead to its functional decline and are associated with diminished ability to meet increased demand. Extensive evidence, derived from both clinical and experimental studies

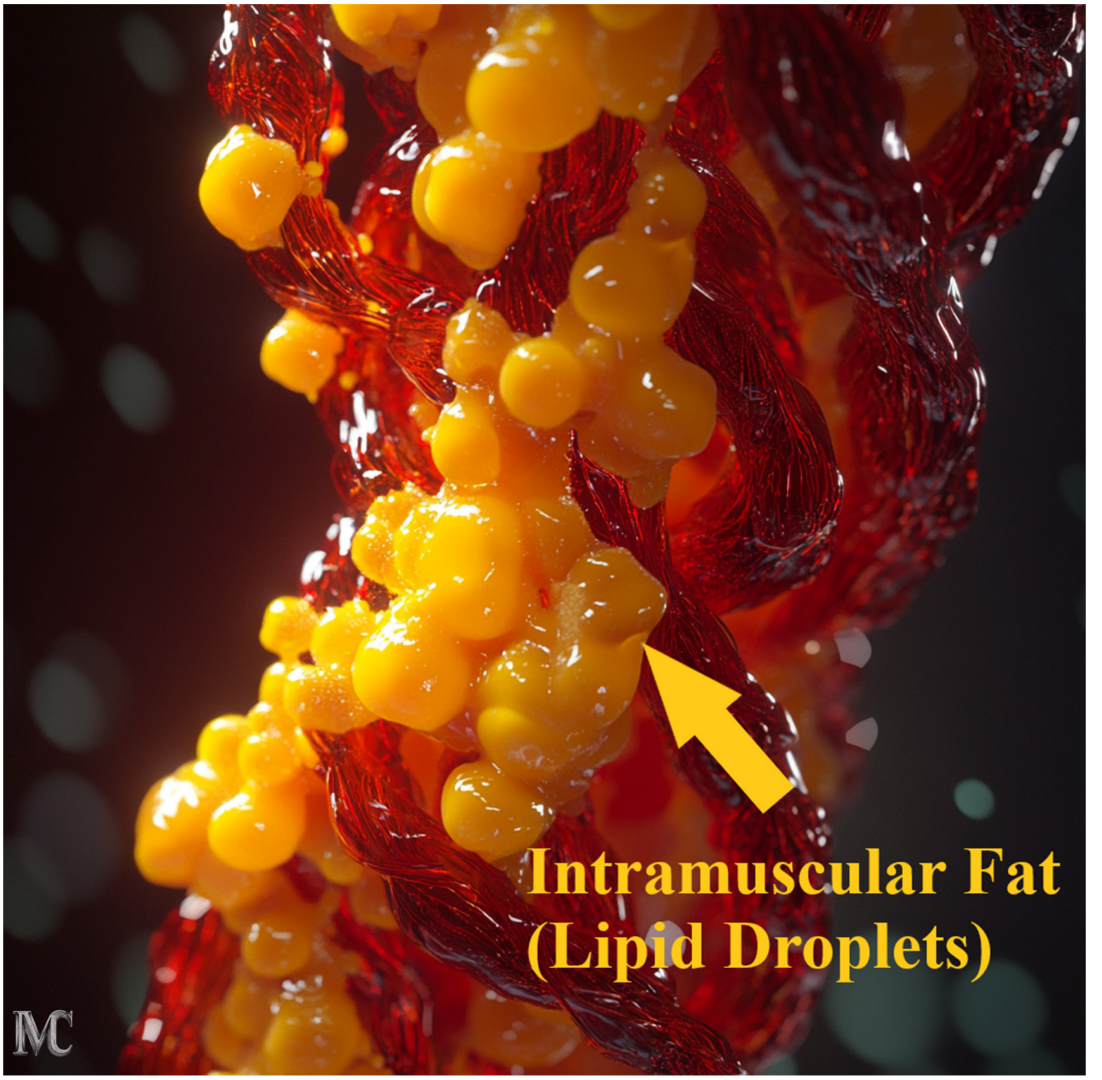
suggests that the aging heart undergoes fibrotic remodeling. Age-dependent accumulation of collagen in the heart leads to progressive increase in ventricular stiffness and impaired diastolic function. Increased mechanical load, due to reduced arterial compliance, and direct senescence-associated fibrogenic actions appear to be implicated in the pathogenesis of cardiac fibrosis in the elderly.
<>Evolving evidence suggests that activation of several distinct molecular pathways may contribute to age-related fibrotic cardiac remodeling. Reactive oxygen species, chemokine-mediated recruitment of mononuclear cells and fibroblast progenitors, transforming growth factor (TGF)-β activation, endothelin-1 and angiotensin II signaling mediate interstitial and perivascular fibrosis in the senescent heart. Reduced collagen degradation may be more important than increased *de novo* synthesis in the pathogenesis of aging-associated fibrosis.
<>In contrast to the baseline activation of fibrogenic pathways in the senescent heart, aging is associated with an impaired reparative response to cardiac injury and defective activation of reparative fibroblasts in response to growth factors. Because these reparative defects result in defective scar formation, senescent hearts are prone to adverse dilative remodeling following myocardial infarction. Understanding the pathogenesis of interstitial fibrosis in the aging heart and dissecting the mechanisms responsible for age-associated healing defects following cardiac injury are critical in order to design new strategies for prevention of adverse remodeling and heart failure in elderly patients."[67.1]

[2] "While it has long been postulated that exercise training attenuates the age-related decline in heart function normally associated with increased fibrosis and collagen cross-linking, the potential benefits associated with exercise training initiated later in life are currently unclear. To address this question, Fischer 344 × Brown Norway F1 rats underwent treadmill-based exercise training starting in late middle age and continued into senescence (35 mo) and were compared with age-matched sedentary rats. Hearts were examined for fibrosis and advanced glycation end-products in the subendocardial layer of left ventricular cross-sections. Genes for collagen synthesis and degradation were assessed by polymerase chain reaction, and matrix metalloproteinase (MMP) activity was assessed by EnzChek® Gelatinase/Collagenase Assay Kit. Exercise training of late middle-aged rats attenuated fibrosis and collagen cross-linking, while also reducing age-related mortality between late middle age and senescence. This training was also associated with an attenuated advanced glycation end-product (AGE) accumulation with aging, suggesting a decrease in collagen cross-linking. Conversely, tissue inhibitor of matrix metalloproteinase-1 (TIMP1) gene expression, TIMP and MMP1 protein expression, and MMP activity increased with age but were not significantly impacted by exercise training. While our results demonstrate that exercise training in late middle age attenuates age-related mortality and cardiac fibrosis and is accompanied by attenuated AGE accumulation indicative of less collagen cross-linking, the mechanisms explaining this attenuated replacement fibrosis did not appear to involve altered TIMP1 expression, or MMP protein and activity."[67.2]

Muscle Lipid Accumulation

AKA Interstitial fat, Intramyocellular lipids, Intramuscular (IM) fat.

Another factor in muscle atrophy being related to obesity, improper supplementation, or ageing. These lipids (ceramides) cause insulin resistance and blunt myogenic signaling (mTOR, IGF-1). AMPK reduces intramuscular lipids[B], alongside Quercetin, Cannabidiol, Chromium, and Betaine [See: Anti-Inflammation Cycle Supplementation]. Certain fatty acids such as Palmitic/Oleic acid [C], and Fasted Endurance Training reduces IM Lipid content [D].



Intramuscular lipids serve the role of providing close-proximity emergency fuel to muscle fibers, which is why fasted cardiovascular training results in enhanced IM fat breakdown, and why fasting paradoxically causes IM lipid accumulation.

Many bodybuilders have suggested that IM fat is beneficial to muscle size or function, but this is simply untrue, as IM fat is lipid droplets within muscle tissue, and **lipid droplets are not adipocytes**, they will not magnify myogenesis by excreting inflammatory chemicals (adipokines), they will only dampen and delay muscular biochemical signaling and regeneration.

You can grow your adipocytes to therefore enhance their excretory activity through careful overfeeding (bulking) to minimize IM fat accumulation, and you can also grow your adipocytes while accumulating large amounts of IM fat by eating high palmitic acid, fructose, or processed foods, alongside high oleic acid meats and vegetable oils, which aligns with the scientifically illiterate and vague suggestion posited by fitness influencers and strength coaches to simply "Eat more calories to grow more muscle".

I believe it is plausible to posit that one reason why burning fat is difficult or seems impossible for certain obese individuals, ones who are on stringent diets, and intense exercise protocols, is that because most individuals engage in exercise in a fed state, they miss the opportunity to target intramuscular fat during lipolysis, and instead their bodies mobilize energy from the largest areas of adipose tissue, often the stomach, and the thighs, while their intramuscular fat content may increase through the overconsumption of "healthy fats", Avocado oils (Oleic acid / Palmitic acid) especially. These intramuscular lipid droplets accumulate while overall body decreases, but after a certain lipid droplet threshold is reached total body lipolysis becomes inefficient and the released energy from triglycerides are only recycled into new triglyceride molecules, due to intramuscular lipid droplet-induced insulin resistance, causing plateaus in weight loss, or *Lipolytic Lag*.

[A] Ceramide synthesis inhibitors enhance myogenesis. Here we have a preview of the next generation of myogenic chemicals.

"<>In L6 skeletal myoblasts induced to differentiate by Arg8-vasopressin treatment, a short-lived lowering of ceramide levels was observed, followed by a long-lasting elevation that was prevented by inhibitors of the de novo synthesis pathway, fumonisin B1 and myriocin. Both inhibitors increased the expression of myogenic differentiation markers and cell fusion rate, whereas short-chain ceramides inhibited these responses. Similar drug effects were observed on primary mouse satellite cell differentiation. Furthermore, bacterial sphingomyelinase overexpression suppressed myogenin nuclear accumulation in L6 cells.
<>These data suggested that endogenous ceramide mediates a negative feedback mechanism limiting myogenic differentiation, and that inhibitors of ceramide synthesis promoted myogenesis by removing this control. Phospholipase D (PLD), a recognized target of ceramide, is required for myogenesis, as shown by the negative effects of PLD1 isoform depletion obtained by siRNA treatment. Fumonisin induced an increase in PLD activity of L6 cells, whereas C6-ceramide decreased it.
<>The expression of PLD1 mRNA transcripts was selectively decreased by C6-ceramide, and increased by ceramide synthesis inhibitors. An early step of myogenic response is the

PLD1-dependent formation of actin stress fiber-like structures. C6-ceramide addition or overexpression of sphingomyelinase impaired actin fiber formation. Ceramide might thus regulate myogenesis through downregulation of PLD1 expression and activity."[68]

[B] AMPK expression decreases muscle lipid accumulation.

"<>Skeletal muscle plays important roles in whole-body energy homeostasis. Excessive skeletal muscle lipid accumulation is associated with some metabolic diseases such as obesity and Type 2 Diabetes. The energy sensor AMPK (AMP-activated protein kinase) is a key regulator of skeletal muscle lipid metabolism, but the precise regulatory mechanism remains to be elucidated. Here, we provide a novel mechanism by which AMPK regulates skeletal muscle lipid accumulation through fat mass and obesity-associated protein (FTO)-dependent demethylation of N^6-methyladenosine (m^6A). <>We confirmed an inverse correlation between AMPK and skeletal muscle lipid content. Moreover, inhibition of AMPK enhanced lipid accumulation, while activation of AMPK reduced lipid accumulation in skeletal muscle cells. Notably, we found that mRNA m^6A methylation levels were inversely correlated with lipid content in skeletal muscle. Furthermore, AMPK positively regulated the m^6A methylation levels of mRNA, which could negatively regulate lipid accumulation in C2C12. At the molecular level, we demonstrated that AMPK regulated lipid accumulation in skeletal muscle cells by regulating FTO expression and FTO-dependent demethylation of m^6A. <>Together, these results provide a novel regulatory mechanism of AMPK on lipid metabolism in skeletal muscle cells and suggest the possibility of controlling skeletal muscle lipid deposition by targeting AMPK or using m^6A related drugs.[69]

[C] Palmitic acid & Oleic acid cause IM Lipid accumulation.

"Conversely, PA or OA exposure induced the intracellular accumulation of lipid droplets and decreased multinucleated myotubes and creatine kinase, inhibited differentiation to skeletal cells and promoted the tans-differentiation to adipocytes of myoblast."[70]

[D] Fasted endurance training promotes intramuscular lipid breakdown.

"<>Training with limited carbohydrate availability can stimulate adaptations in muscle cells to facilitate energy production via fat oxidation. Here we investigated the effect of consistent training in the fasted state, vs. training in the fed state, on muscle metabolism and substrate selection during fasted exercise. Twenty young male volunteers participated in a 6-wk endurance training program (1-1.5 h cycling at ~70% Vo_2max), 4 days/wk) while receiving isocaloric carbohydrate-rich diets. Half of the subjects trained in the fasted state (F; n = 10), while the others ingested ample carbohydrates before (~160 g) and during (1 g·kg body $wt^{-1}·h^{-1}$) the training sessions (CHO; n = 10). <>The training similarly increased Vo_2max) (+9%) and performance in a 60-min simulated time trial (+8%) in both groups ($P < 0.01$). Metabolic measurements were made during a 2-h constant-load exercise bout in the fasted state at ~65% pretraining

Vo(2max). In F, exercise-induced intramyocellular lipid (IMCL) breakdown was enhanced in type I fibers ($P < 0.05$) and tended to be increased in type IIa fibers ($P = 0.07$). Training did not affect IMCL breakdown in CHO. In addition, F (+21%) increased the exercise intensity corresponding to the maximal rate of fat oxidation more than did CHO (+6%) ($P < 0.05$). Furthermore, maximal citrate synthase (+47%) and β-hydroxyacyl coenzyme A dehydrogenase (+34%) activity was significantly upregulated in F ($P < 0.05$) but not in CHO. Also, only F prevented the development exercise-induced drop in blood glucose concentration ($P < 0.05$). In conclusion, F is more effective than CHO to increase muscular oxidative capacity and at the same time enhances exercise-induced net IMCL degradation. In addition, F but not CHO prevented drop of blood glucose concentration during fasting exercise."[71]

[E] A High Fat / High Fructose Diet promotes intramuscular lipid accumulation, excluding polyunsaturated fatty acids.

"<>Metabolic syndrome components, including obesity, dyslipidemia and impaired glucose homeostasis, become a major public health issue. Muscles play a predominant role in insulin-mediated glucose uptake, and high fat diets may negatively affect muscle function and homeostasis. This work aimed to study the time-course of muscle lipid accumulation, oxidative stress and mitochondrial dysfunction and their association to impaired glucose homeostasis in rats fed an obesogenic diet. Male Wistar rats were fed with a standard or a high fat/high fructose (HFHFr) diet and sacrificed on 4, 8, 12, 16, 20 weeks.
<>Rats fed the HFHFr diet developed mild overweight, increased liver and adipose tissue weights and glucose intolerance. The impaired glucose homeostasis increased gradually with the HFHFr diet to become significant on the 12th and 16th weeks of diet. In parallel, the muscle lipid composition showed an increase in the saturated fatty acids and the monounsaturated fatty acids with a marked decrease in the polyunsaturated fatty acids.
<>The HFHFr diet also increased muscle contents of both diacylglycerols and Ceramides. Surprisingly, HFHFr diet did not induce major muscle mitochondrial dysfunction or oxidative stress.
<>These results indicate that muscle lipid alterations, as well as impaired glucose homeostasis occur as early as the 8th week of HFHFr diet, increase to reach a plateau around the 12th-16th weeks of diet, and then attenuate towards the end of study. At these diet treatment durations, muscle mitochondrial activity and oxidative stress remained unchanged and do not seem to have a major role in the observed impaired glucose homeostasis."[72]

[E2] Fructose is one common cause of Ceramide accumulation in the body, and Insulin Resistance, through altering the gut microbiome negatively.

"<>Objective: The link between metabolic derangement of the gut-2013liver-visceral white adipose tissue (v-WAT) axis and gut microbiota was investigated. Methods: Rats were fed a fructose-rich diet and treated with an antibiotic mix. Inflammation was

measured in portal plasma, ileum, liver, and v-WAT, while insulin signalling was analysed by measuring levels of phosphorylated kinase Akt. The function and oxidative status of hepatic mitochondria and caecal microbiota composition were also evaluated.
<>Results: Ileal inflammation, increase in plasma transaminases, plasma peroxidised lipids, portal concentrations of tumour necrosis factor alpha, lipopolysaccharide, and non-esterified fatty acids, were induced by fructose and were reversed by antibiotic. The increased hepatic ceramide content, inflammation and decreased insulin signaling in liver and v-WAT induced by fructose was reversed by antibiotic. Antibiotic also blunted the increase in hepatic mitochondrial efficiency and oxidative damage of rats fed fructose-rich diet. Three genera, Coprococcus, Ruminococcus, and Clostridium, significantly increased, while the Clostridiaceae family significantly decreased in rats fed a fructose-rich diet, and antibiotic abolished these variations.
<>Conclusions: When gut microbiota modulation by fructose is prevented by antibiotic, inflammatory flow from the gut to the liver and v-WAT are reversed."[73]

[F] Ceramide synthesis in skeletal muscle requires the inflammatory Toll like 4 Receptors.

"<>Toll-like receptor 4 (TLR4) is a proposed mediator of ceramide accumulation, muscle atrophy, and insulin resistance in skeletal muscle. It is currently unknown whether pharmacological inhibition of TLR4, using the TLR4-specific inhibitor TAK-242 during muscle disuse, is able to prevent changes in intracellular ceramide species and consequently preserve muscle size and insulin sensitivity in physically active mice. To address this question, we subjected running wheel-conditioned C57BL/6 male mice (13 wk old; ~10/group) to 7 days of hindlimb suspension (HS), 7 days of continued wheel running (WR), or daily injections of TAK-242 during HS (HS + TAK242) for 7 days.
<>We measured hindlimb muscle morphology, intramuscular and liver ceramide content, HOMA-IR, mRNA proxies of ceramide turnover and lipid trafficking, and muscle fatty acid and glycerolipid content. As a result, soleus and liver ceramide abundance was greater ($P < 0.05$) in HS vs. WR but was reduced with TLR4 inhibition (HS + TAK-242 vs. HS). Muscle mass declined ($P < 0.01$) with HS (vs. WR), but TLR4 inhibition did not prevent this loss (soleus: $P = 0.08$; HS vs. HS + TAK-242). HOMA-IR was impaired ($P < 0.01$) in HS versus WR mice, but only fasting blood glucose was reduced with TLR4 inhibition (HS + TAK-242 vs HS, $P < 0.05$). Robust decreases in muscle Spt2 and Cd36 mRNA and muscle lipidomic trafficking may partially explain reductions in ceramides with TLR4 inhibition.
<>In conclusion, pharmacological TLR4 inhibition in wheel-conditioned mice prevented ceramide accumulation during the early phase of hindlimb suspension (7 days) but had little effect on muscle size and insulin sensitivity."[74]

[G] High glucose conditions (without insulin present) stimulate skeletal muscle stem cell conversion to adipocytes. Although this study goes on to suggest ROS as the prime mediator of glucose-induced adipogenesis, it's not in line with the previous research. The importance of this study is to illustrate the dangers of consuming excess carbohydrates as

an athlete, as it will undoubtedly decrease the stem cell pool in favor of adipogenesis over myogenesis.

"<>Regeneration of mesenchymal tissues depends on a resident stem cell population, that in most cases remains elusive in terms of cellular identity and differentiation signals. We here show that primary cell cultures derived from adipose tissue or skeletal muscle differentiate into adipocytes when cultured in high glucose. High glucose induces ROS production and PKCβ activation. These two events appear crucial steps in this differentiation process that can be directly induced by oxidizing agents and inhibited by PKCβ siRNA silencing. The differentiated adipocytes, when implanted in vivo, form viable and vascularized adipose tissue.
<>Overall, the data highlight a previously uncharacterized differentiation route triggered by high glucose that drives not only resident stem cells of the adipose tissue but also uncommitted precursors present in muscle cells to form adipose depots. This process may represent a feed-forward cycle between the regional increase in adiposity and insulin resistance that plays a key role in the pathogenesis of diabetes mellitus."[74.A]

[See: Joint Health Supplementation: Glucosamine]

Stem Cell Senescence

Satellite cells are located within myofibers, they mobilize in response to injury to repair damaged muscle tissue. As we age, many of our satellite cells lose the ability to function, to divide, and grow—this is *Cellular Senescence*. Cellular Senescence should not be confused with Cellular Quiescence, as the former process is primarily, until advanced medicine solves the issue, a permanent change to cellular function due to damage, whereas Cellular Quiescence is a reversible change to cellular function, most often associated with the different stages of wound healing (myogenesis).

Senescence Cells secrete inflammatory chemicals such as IL-1B, IL-6, TNF-a, and ROS, and this is called the "Senescence-associated Secretory Phenotype" (SASP). As we age, and accumulate damaged, senescent cells, our basal levels of inflammation increase progressively, making it necessary to reduce inflammation in the body through antioxidant use, and take better care to avoid environmental toxins which will only accelerate our biological decay.

In the study below[1] by Chanhee Kang, & Stephen J. Elledge, we learn that there are two forms of autophagy, *Selective Autophagy*, and *General Autophagy*. Selective Autophagy exerts an antisenescence effect through the selective autophagic breakdown of accumulated cellular GATA4 protein, which if left unchecked results in NF-κB activation and the cellular switch to SASP, whereas General Autophagy promotes a prosenescence effect by way of causing a paradoxical rise in mTOR activity through interacting with TOR-autophagy spatial coupling compartment (TASCC) in the cell, where amino acids broken down during autophagy are recycled and accumulate, leading to mTOR activation, and the release of SASP factors.

Importantly, this complicated cascade of intracellular events will not occur under "normal" conditions, wherein cells are not damaged into senescence, meaning that General Autophagy will not have any negative consequences if intermittently experienced during youth, such as during intermittent fasting, and exercise.

[1] "<>Cellular senescence is a terminal arrest of proliferation triggered by various cellular stresses including dysfunctional telomeres, DNA damage, oxidative stress, and oncogenic mutations. Senescence not only prevents the proliferation of damaged cells, thereby preventing tumorigenesis, but also affects the microenvironment through the secretion of pro-inflammatory cytokines, chemokines, growth factors, and proteases, a feature termed the senescence-associated secretory phenotype (SASP). The SASP increases immune surveillance of damaged cells, thus maintaining tissue homeostasis. With age or persistent damage, however, the SASP from accumulated senescent cells is thought to cause chronic inflammation that may contribute to many human diseases including cancer. In addition to the cell cycle and the SASP, the senescence program also controls other cellular processes and among these is the activation of macroautophagy (hereafter autophagy). Autophagy is an intracellular degradation system that plays a wide variety of physiological and pathophysiological roles, which are sometimes complex. Several studies have indicated that this is also the case for cellular senescence.
<>The first causal relationship between autophagy and senescence came from oncogene-induced senescence (OIS), showing that autophagy inhibition delays HRASG12V-induced senescence and the SASP. Through a specialized compartment known as the TOR-autophagy spatial coupling compartment (TASCC), autophagy generates a high flux of recycled amino acids and other metabolites, which are subsequently used by MTORC1 for supporting the massive synthesis of the SASP factors and facilitating senescence. However, in contrast to this positive relationship, it has also been reported that autophagy inhibition induces or promotes cellular senescence in normal proliferating cells and paradoxically during HRASG12V-induced senescence, respectively. At least in the former case, increased levels of reactive oxygen species upon autophagy inhibition partially contribute to cellular senescence, indicating the important roles of autophagy in cellular homeostasis. Is there a molecular mechanism that could resolve these apparently conflicting reports about the relationship between autophagy and cellular senescence? One potential explanation is that autophagy may modulate several targets that act in an opposite manner to regulate cellular senescence. Thus, autophagy inhibition could result in different outcomes depending on the timing, duration, or type of its inhibition. Our recent findings suggest this may in fact be the case.
<>While exploring regulators of cellular senescence, we identified a transcription factor, GATA4, as a key regulator of the SASP and senescence. GATA4 accumulates during cellular senescence, mainly due to its increased protein stability. Interestingly, we found that GATA4 stability is regulated by autophagy. The autophagic receptor protein SQSTM1/p62 mediates the degradation of GATA4 under normal conditions. However, once the cell experiences senescence-inducing stimuli, the interaction between GATA4 and SQSTM1 decreases, and GATA4 escapes from autophagic inhibition and accumulates. This accumulated GATA4 initiates a transcriptional circuit to activate

NFKB/NF-κB and the SASP. Senescence induction also increases general autophagy, which contributes to the SASP and cellular senescence through the TASCC. We showed this by temporal regulation of autophagy; transient inhibition of autophagy using an inducible shRNA system causes senescence more efficiently than does continuous inhibition. These data were further supported by the fact that SQSTM1 depletion induces cellular senescence more effectively than does depletion of core autophagy regulators, ATG7 or ATG5, under normal conditions. <>Together, these data suggest that selective autophagy actively suppresses cellular senescence through the degradation of a senescence regulator, GATA4, whereas general autophagy supports senescence transition through the TASCC. Thus, autophagy can act through either an anti- or prosenescence mechanism depending on its type of regulation.

<>How the interaction between GATA4 and SQSTM1 is regulated is currently unknown. However, we found that GATA4 activation depends on the DNA damage response (DDR) kinases, ATM and ATR, during cellular senescence, suggesting that ATM and ATR regulate the selective autophagy of GATA4. Based on recent findings that phosphorylation of SQSTM1 affects the affinity between SQSTM1 and its substrates, it would be interesting to examine whether ATM and ATR directly phosphorylate either SQSTM1 or GATA4 to decrease their interaction. Another possibility is that ATM and ATR modulate a signal transducer that can regulate the interaction between GATA4 and SQSTM1. SQSTM1 primarily recognizes ubiquitinated substrates, thus either E3 ubiquitin ligases or deubiquitinating enzymes could be involved as a signal transducer. Alternatively, it is possible that other substrates for SQSTM1 increase in an ATM- and ATR-dependent manner during senescence, which outcompete GATA4 for binding with SQSTM1. This is a question for future experiments, as it will provide further information on how autophagy and cellular senescence are intertwined and how the DDR regulates selective autophagy.

<>Another key question is how general autophagy increases during cellular senescence. One potential mechanism for this regulation would be a key senescence regulatory pathway, the TP53/p53 pathway. Activation of TP53 initiates cell cycle arrest during cellular senescence. This activation, however, is sustained at intermediate levels even after cell cycle arrest is reinforced by the subsequent activation of the CDKN2A/p16 pathway, suggesting that the TP53 pathway may have additional roles beyond cell cycle arrest during senescence. Previous studies have shown that nuclear TP53 can activate transcription of several autophagy-related genes including ULK1, ATG5, and ATG7. Therefore, sustained TP53 activation might contribute to the activation of general autophagy during cellular senescence.

<>In summary, the regulation of GATA4 provides an explanation for the conundrum of how autophagy acts in one instance to promote senescence but in another to prevent it. This finding reconciles the conflicting reports and clarifies the complex relationship between autophagy and cellular senescence by showing that basal, selective autophagy acts as an antisenescence mechanism, whereas general autophagy acts as a prosenescence mechanism."[74.0]

[B] Autophagy is activated following the switch to senescence, and this cellular switch can be partially suppressed through autophagy inhibition, meaning that in the elderly, those of whom are likely to have a larger population of senescent cells, it is of absolute necessity to ensure their protein intake is high, to stimulate mTOR, and mitigate autophagy, thereby preventing the inflammatory secretion of senescent cells. For those of greater age who are healthy, and resilient physically and mentally, there is no need to increase or monitor protein intake, as they do not display signs of chronic senescence. Although mTOR causes senescence, excessive autophagy is no better for the body, complicating the matter of efficient life extension and of graceful aging. I can simplify this issue by suggesting that *prolonged* fasting, and any form of dietary protein restriction be reserved for young individuals only.

"<>As a stress response, senescence is a dynamic process involving multiple effector mechanisms whose combination determines the phenotypic quality. Here we identify autophagy as a new effector mechanism of senescence. Autophagy is activated during senescence and its activation is correlated with negative feedback in the PI3K-mammalian target of rapamycin (mTOR) pathway. A subset of autophagy-related genes are up-regulated during senescence: Overexpression of one of those genes, ULK3, induces autophagy and senescence.
<>Furthermore, inhibition of autophagy delays the senescence phenotype, including senescence-associated secretion. Our data suggest that autophagy, and its consequent protein turnover, mediate the acquisition of the senescence phenotype."[74.1]

[C] High Intensity Cardiovascular Exercise or High Volume Lactate-inducing exercise delays muscle cell senescence (p16 marker).

"<>The intensity effects of aerobic exercise on cellular senescence and DNA repair response of human skeletal muscle have not been previously documented. In this study, the major findings are as follows:
<> (1) Cellular senescence-lowering effect of aerobic exercise can occur only at high intensity. SSE with similar exercise work failed to lower the p16INK4a mRNA in human skeletal muscle within the 24-h recovery period;
<>(2) HIIE triggered immediate increases in cell infiltration and γ-H2AX+ myofibers, followed by a decreased p16INK4a mRNA in human skeletal muscle 24 h after recovery;
<> (3) By further examining the individual responses, the senolytic effect of HIIE were contributed solely from those participants with high pre-exercise p16INK4a mRNA in skeletal muscles. High intensity exercise is known to cause greater levels of lactate production and acidosis than low intensity exercise. Decreased pH has been reported to be a danger signal to activate innate immune response and immune cells are functioned to recognize and clear senescent cells by phagocytosis in humans. <>Therefore, the acute changes in the microenvironment during and after exercise may be a selection pressure to aged stem cell population resided in the skeletal muscle. Exercise intensity determines the magnitude of cell renewal during a brief period of inflammation."[74.2]

[C2] Endurance Training promotes Satellite Cell self-renewal by suppressing differentiation through a reduced mitochondrial respiration mechanism, meaning that high volume aerobics and Endurance Training is capable of delaying the aging of skeletal muscle stem cells. Whether this effect of enhanced stemness would be perturbed by the consumption of intra-exercise carbohydrates, I do not know, but we can safely surmise that the mice in this study were not provided a miniature CamelBak hydration pack containing Gatorade with an attached dripper tube. Therefore, to mimic this study accurately one would be suggested to withhold carbohydrates for post-exercise consumption only.

"<>Background: Skeletal muscle stem cells (satellite cells) are well known to participate in regeneration and maintenance of the tissue over time. Studies have shown increases in the number of satellite cells after exercise, but their functional role in endurance training remains unexplored.
<>Methods: Young adult mice were submitted to endurance exercise training and the function, differentiation, and metabolic characteristics of satellite cells were investigated in vivo and in vitro.
<>Results: We found that injured muscles from endurance-exercised mice display improved regenerative capacity, demonstrated through higher densities of newly formed myofibres compared with controls (evidenced by an increase in embryonic myosin heavy chain expression), as well as lower inflammation (evidenced by quantifying CD68-marked macrophages), and reduced fibrosis. Enhanced myogenic function was accompanied by an increased fraction of satellite cells expressing self-renewal markers, while control satellite cells had morphologies suggestive of early differentiation. The beneficial effects of endurance exercise were associated with satellite cell metabolic reprogramming, including reduced mitochondrial respiration (O2 consumption) under resting conditions (absence of muscle injury) and increased stemness. During proliferation or activated states (3 days after injury), O2 consumption was equal in control and exercised cells, while exercise enhanced myogenic colony formation. Surprisingly, inhibition of mitochondrial O2 consumption was sufficient to enhance muscle stem cell self-renewal characteristics in vitro. Moreover, transplanted muscle satellite cells from exercised mice or cells with reduced mitochondrial respiration promoted a significant reduction in inflammation compared with controls.
<>Conclusions: Our results indicate that endurance exercise promotes self-renewal and inhibits differentiation in satellite cells, an effect promoted by metabolic reprogramming and respiratory inhibition, which is associated with a more favourable muscular response to injury."[74.2.1]

[D] AMPK delays Tendon stem cell aging.

"<>Age-related tendon disorders are closely linked with tendon stem/progenitor cell (TSPC) senescence. However, the underlying mechanisms of TSPC senescence and promising therapeutic strategies for rejuvenation of TSPC senescence remain unclear. In this study, the senescent state of TSPCs increased with age. It was also verified that the

AMPK inhibition/mTOR activation is correlated with the senescent state of TSPCs. Furthermore, a low dose of metformin mitigated TSPC senescence and restored senescence-related functions, including proliferation, colony-forming ability, migration ability and tenogenic differentiation ability at the early stage of aging.
<>The protective effects of metformin on TSPCs were regulated through the AMPK/mTOR axis. An in vivo study showed that metformin treatment postpones tendon aging and enhances AMPK phosphorylation but reduces mTOR phosphorylation in a natural aging rat model.
<>Our study revealed new insight and mechanistic exploration of TSPC senescence and proposed a novel therapeutic treatment for age-related tendon disorders by targeting the AMPK/mTOR axis at the early stage of aging."[74.3]

[D2] Tendon AMPK activity is suppressed by high glucose conditions, whereas low glucose conditions increase tendon AMPK activity.

"<>Diabetes mellitus (DM) is associated with higher risk of tendinopathy, which reduces tolerance to exercise and functional activities and affects lifestyle and glycemic control. Expression of tendon-related genes and matrix metabolism in tenocytes are essential for maintaining physiological functions of tendon. However, the molecular mechanisms involved in diabetic tendinopathy remain unclear. We hypothesized that high glucose (HG) alters the characteristics of tenocyte.
<>Using in vitro 2-week culture of tenocytes, we found that expression of tendon-related genes, including Egr1, Mkx, TGF-β1, Col1a2, and Bgn, was significantly decreased in HG culture and that higher glucose consumption occurred. Down-regulation of Egr1 by siRNA decreased Scx, Mkx, TGF-β1, Col1a1, Col1a2, and Bgn expression. Blocking AMPK activation with Compound C reduced the expression of Egr1, Scx, TGF-β1, Col1a1, Col1a2, and Bgn in the low glucose condition.
<>In addition, histological examination of tendons from diabetic mice displayed larger interfibrillar space and uneven glycoprotein deposition. Thus, we concluded that high glucose alters tendon homeostasis through downregulation of the AMPK/Egr1 pathway and the expression of downstream tendon-related genes in tenocytes. The findings render a molecular basis of the mechanism of diabetic tendinopathy and may help develop preventive and therapeutic strategies for the pathology."[74.4]

[See: Anti-Inflammation Cycle Supplementation: Silymarin]

[See: Pro-Inflammation Modalities: B.F.R. Training: Hematopoietic Progenitor Cells]

Lactic Acid Training (LAT)

Intramuscular lactate forms when exercising in hypoxic (low oxygen) conditions, predominately during high volume or high intensity exercise, especially volitional exercise to failure. Lactate accumulation during workouts should be sought after, whether

in the beginning or end of the workout, as it facilitates MyoD expression, and fast twitch fiber growth. Loads from 5-30% are suggested for maximal lactate accumulation during exercise. Performing LAT as *Warmups* with very low loads is the best idea because the Central Nervous System is not fatigued, and your pain threshold is highest earliest in the workout.

Many gym goers are unaware of the importance that lactate plays in Myogenesis, they are under the impression that heavy loads are the key to hypertrophy, and in that error, they overtrain, plateau, and sometimes their training progress regresses. There is no point in resistance training with heavy weight if one does not have the motor pathway intelligence and pain tolerance to accumulate intra-muscular lactate through high volume exercise as it is the most myogenic and impressive form of training.

Although it is true that you can accumulate lactic acid in your muscles by lifting higher loads, and this is an excellent way to train when engaging in higher volume regular-speed strength training, you should and must learn to accumulate lactate in your muscles by lifting lower loads, while maintaining near-constant time-under-tension without technique breakdown over the course of dozens of repetitions, because the mastery of low load lactic acid training is the mastery of the motor pathway, and of the mind, where the pain threshold is tested and strengthened in a productive evolutionarily beneficial way.

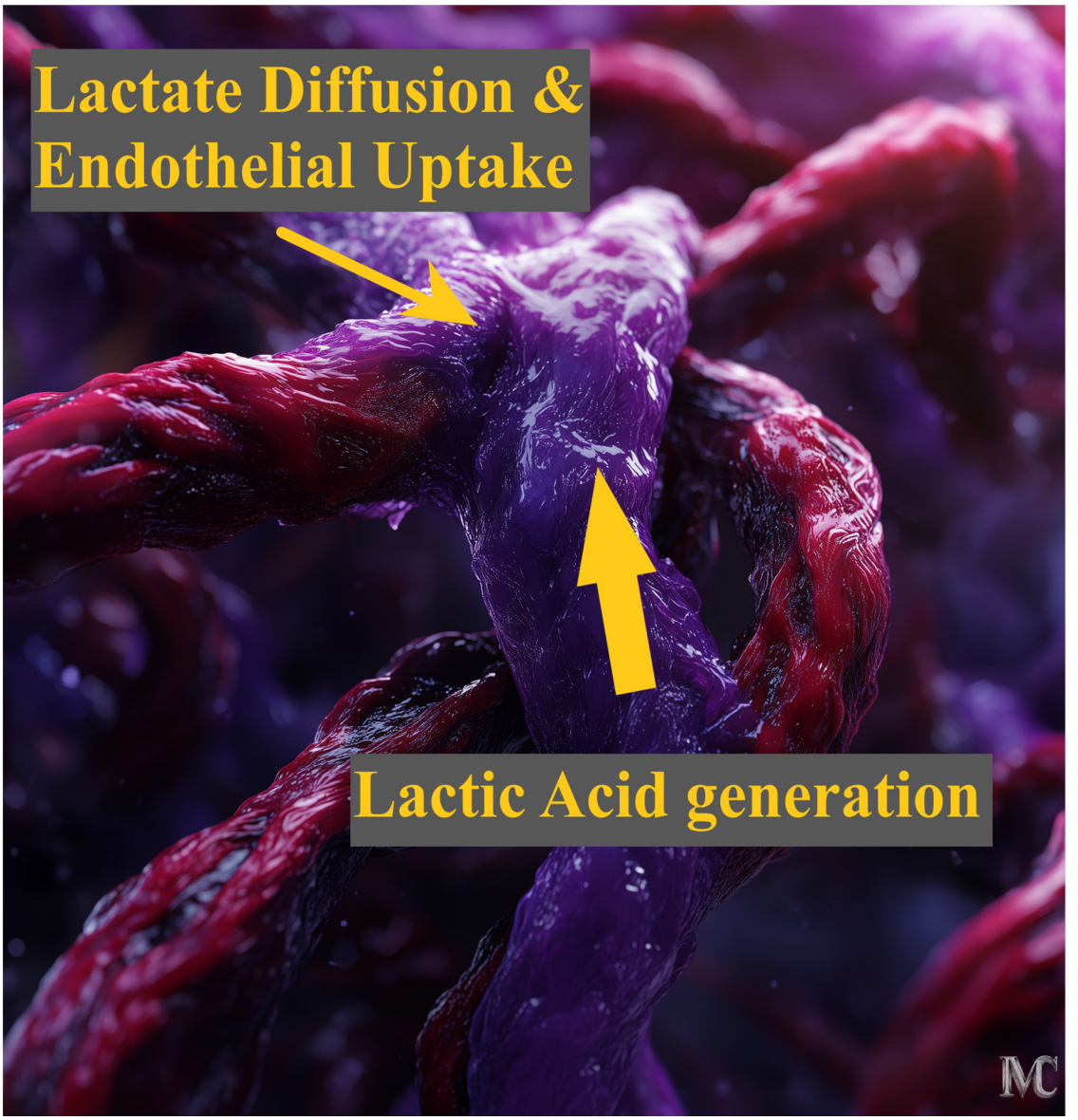
Lactic Acid is not simply a myogenic compound, it diffuses from the muscle tissue and is absorbed by muscle capillaries to travel into systemic circulation, passing the Blood Brain Barrier and stimulating a neurotrophic response, and protecting many different types of cells in our body from inflammation-induced cell death. Lactic Acid is an unrecognized anti-aging factor that athletes of old have for so long conflated with negative effects due to the nerve irritation and pain associated with its acute effects experienced during exercise, which is an unfortunate but psychologically understandable confusion. I believe it is quite obvious that Cardiovascular-based exercise athletes have a higher average IQ as opposed to strength athletes precisely because of Lactic Acid generation, as the less physical pain you experience in a workout, the less neurological benefits you will attain.

Although it is true that glucose can be converted directly to Lactate during Anaerobic (Low Oxygen: High Intensity Exercise) conditions and this may seem to argue in favor of a high carbohydrate diet or the use of intra-workout glucose drinks for generating greater amounts of muscle lactate during a workout, fasted or low blood sugar exercise and resultant glycogen exhaustion will always result in greater lactic acid formation in muscle during shorter duration high intensity exercise (under sixty minutes) because the process of proteolysis and lipolysis are not sufficient to provide muscles with the required energy (ATP) during high intensity exercise, catecholamines are released to maintain blood sugar which leads to the rapid release of glycogen stores, and because insulin levels are lower and cellular energy shuttling is reduced, the body shifts to maximal levels of Anaerobic metabolism during higher intensity forms of exercise in a fasted state.

Because Lactic Acid stimulate MyoD, it is capable of stimulating early myogenic differentiation, but this does not mean that it will interfere with myogenic proliferation, as *this is dependent on sustained muscle damage*, meaning that if a workout does not damage muscle tissue to a great extent, early differentiation will not perturb early

hypertrophy, not by a large margin, but if maximal gains of muscle tissue is your goal, you should detrain for a minimum of 96 Hours after an intense workout of any nature. Considering that Lactic Acid promotes muscle growth through processes beyond MyoD, such as the activation of Erk1/2, P70SK, & 4E-BP1, it is still myogenic towards early hypertrophy.

I believe my term “Lactic Acid Training” is apropos to this new focused mode of training, but I see no reason why we could not call it “Lactate Training” .



Note: If I suggest “Lactic Acid Training” at any following point in this book I am either referring to Lactic Acid Training Warmups (5% 1RM), or Classical Lactic Acid Training (5-30% 1RM).

[A] High Volume, Low Load Training i.e., what I refer to as "**Lactic Acid Training**", enhances Myogenic Proteins, MRF's, & Protein Synthesis more than Low Volume, High Load Training due to an unmentioned by obvious increased Lactate saturation of muscle tissue.

"<>Fifteen men (21±1 years; BMI=24.1±0.8 kg/m2) performed 4 sets of unilateral leg extension exercise at different exercise loads and/or volumes: 90% of repetition maximum (1RM) until volitional failure (90FAIL), 30% 1RM work-matched to 90%FAIL (30WM), or 30% 1RM performed until volitional failure (30FAIL). Infusion of [ring-13C6] phenylalanine with biopsies was used to measure rates of mixed (MIX), myofibrillar (MYO), and sarcoplasmic (SARC) protein synthesis at rest, and 4 h and 24 h after exercise.
<>Exercise at 30WM induced a significant increase above rest in MIX (121%) and MYO (87%) protein synthesis at 4 h post-exercise and at 24 h in the MIX only. The increase in the rate of protein synthesis in MIX and MYO at 4 h post-exercise with 90FAIL and 30FAIL was greater than 30WM, with no difference between these conditions; however, MYO remained elevated (199%) above rest at 24 h only in 30FAIL. There was a significant increase in AktSer473 at 24h in all conditions (P=0.023) and mTORSer2448 phosphorylation at 4 h post-exercise (P=0.025). Phosporylation of Erk1/2Tyr202/204, p70S6KThr389, and 4E-BP1Thr37/46 increased significantly (P<0.05) only in the 30FAIL condition at 4 h post-exercise, whereas 4E-BP1Thr37/46 phosphorylation was greater 24 h after exercise than at rest in both 90FAIL (237%) and 30FAIL (312%) conditions. Pax7 mRNA expression increased at 24 h post-exercise (P=0.02) regardless of condition. The mRNA expression of MyoD and myogenin were consistently elevated in the 30FAIL condition."[75]

[A2] Lactate promotes muscle regeneration and hypertrophy.
"<>Lactate is a metabolic substrate mainly produced in muscles, especially during exercise. Recently, it was reported that lactate affects myoblast differentiation; however, the obtained results are inconsistent, and the in vivo effect of lactate remains unclear. Our study thus aimed to evaluate the effects of lactate on myogenic differentiation and its underlying mechanism. The differentiation of C2C12 murine myogenic cells was accelerated in the presence of lactate and, consequently, myotube hypertrophy was achieved.
<>Gene expression analysis of myogenic regulatory factors showed significantly increased myogenic determination protein (MyoD) gene expression in lactate-treated cells compared with that in untreated ones. Moreover, lactate enhanced gene and protein expression of myosin heavy chain (MHC). In particular, lactate increased gene expression of specific MHC isotypes, MHCIIb and IId/x, in a dose-dependent manner. Using a reporter assay, we showed that lactate increased promoter activity of the MHCIIb gene and that a MyoD binding site in the promoter region was necessary for the lactate-induced increase in activity.
<>Finally, peritoneal injection of lactate in mice resulted in enhanced regeneration and fiber hypertrophy in glycerol-induced regenerating muscles. In conclusion,

physiologically high lactate concentrations modulated muscle differentiation by regulating MyoD-associated networks, thereby enhancing MHC expression and myotube hypertrophy in vitro and, potentially, in vivo."[76]

[A3] Lactate may promote fast twitch fiber growth (EDL) over slow-twitch (Soleus).

"<>Skeletal muscle is described as an endocrine organ, constitutively or intermittently secreting bioactive molecules. The signaling pathways by which these molecules mediate changes in skeletal muscle and regulate interorgan crosstalk are only partly understood. Lactate is widely described as a signaling molecule in different cells, but the role of lactate as a signaling molecule in mature skeletal muscle has not been fully unveiled.
<>The aim of this study was to determine the role of lactate on activation of signaling pathways in adult mouse skeletal muscle. Male mice were injected intraperitoneally with lactate or saline, and tissues were dissected after 40 min. Phosphorylation levels of relevant proteins in muscle were assessed by Western blotting. After lactate administration, we found an increase in p-ERK1/2Thr202/Tyr204 (3.5-fold; P = 0.004) and p-p70S6KThr389 (1.9-fold; P = 0.01) in quadriceps; and an increase in p-rpS6Ser235/236 in both quadriceps (6.3-fold; P = 0.01) and EDL (2.3-fold; P = 0.01), without changes in soleus. There was a tendency toward an increase in p-AMPKThr172 (1.7-fold; P = 0.08), with a significant increase in p-ACCSer79 (1.5-fold; P = 0.04) in soleus, without changes in quadriceps and EDL.
<>These results support the hypothesis that lactate plays a role in the molecular signaling related to hypertrophy and to oxidative metabolism on adult skeletal muscle and suggest that this activation depends on the skeletal muscle type. The mechanisms that underlie the effect of lactate in mature skeletal muscles remain to be established."[77]

[B] Lactic Acid promotes bDNF expression through activation of Sirtuin-1. This is one explanation for the greater and more functional intelligences of those who specialize in cardiovascular exercise, versus those who specialize in strength sports.

"<>Exercise promotes learning and memory formation. These effects depend on increases in hippocampal BDNF, a growth factor associated with cognitive improvement and the alleviation of depression symptoms. Identifying molecules that are produced during exercise and that mediate hippocampal Bdnf expression will allow us to harness the therapeutic potential of exercise.
<>Here, we report that an endogenous molecule produced during exercise in male mice induces the Mus musculus Bdnf gene and promotes learning and memory formation. The metabolite lactate, which is released during exercise by the muscles, crosses the blood-brain barrier and induces Bdnf expression and TRKB signaling in the hippocampus. Indeed, we find that lactate-dependent increases in BDNF are associated with improved spatial learning and memory retention. The action of lactate is dependent on the activation of the Sirtuin1 deacetylase. SIRT1 increases the levels of the transcriptional coactivator PGC1a and the secreted molecule FNDC5, known to mediate Bdnf expression. These results reveal an endogenous mechanism to explain how physical

exercise leads to the induction of BDNF, and identify lactate as a potential endogenous molecule that may have therapeutic value for CNS diseases in which BDNF signaling is disrupted.
<>SIGNIFICANCE STATEMENT It is established that exercise promotes learning and memory formation and alleviates the symptoms of depression. These effects are mediated through inducing Bdnf expression and signaling in the hippocampus. Understanding how exercise induces Bdnf and identifying the molecules that mediate this induction will allow us to design therapeutic strategies that can mimic the effects of exercise on the brain, especially for patients with CNS disorders characterized by a decrease in Bdnf expression and who cannot exercise because of their conditions. We identify lactate as an endogenous metabolite that is produced during exercise, crosses the blood-brain barrier and promotes hippocampal dependent learning and memory in a BDNF-dependent manner. Our work identifies lactate as a component of the "exercise pill.""[77.A]

[C] Lactic Acid exerts an acute immunosuppressive effect on the body through M1 polarization inhibition, which may predispose one to cancer generation, but this is not to be a concern for those on an Anti-Cycle. It appears that fast twitch fibers truly prefer an anti-inflammatory biological milieu, which ties in to detraining, as inflammation quells during the late stages of myogenesis and the progression towards hyperplasia.

"<>Although lactic acid has been known to inhibit inflammatory response, mechanisms underlying the inhibitory effect remain poorly understood. To define this lactic acid effect, we used the activation by LPS of bone-marrow-derived macrophages (BMDMs) and found that lactic acid at concentrations as low as 10 mM significantly inhibited pro-inflammatory cytokine expression and production. We then asked whether lactic acid inhibits LPS signaling (i.e., TLR4 signaling). However, lactic acid, even at higher concentrations (i.e., >10 mM), had no effect on the activation of nuclear factor κB (NF-κB) and p38 mitogen-activated protein (MAP) kinase pathways in macrophages as well as 293T cells overexpressing NF-κB reporter. A kinetic experiment also showed that the inhibitory effect of lactic acid was found to occur as early as 1 h on the pro-inflammatory cytokine response, but not the LPS signaling. These data suggest that the anti-inflammatory effect of lactic acid is not mediated via the inhibition of canonical LPS signaling."
↓ continued
"<>Lactic acid has emerged as an important modulator of the immune system. High lactic acid concentrations in tissue microenvironments such as tumors and intestines are sufficient to exert immunosuppressive activity on both innate and adaptive immune cells. During infection or tissue injury, lactic acid regulates macrophage metabolism and prevents excessive inflammatory response; in tumors, lactic acid produced by tumor cells promotes the polarization of TAMs, which in turn promotes tumor progression.
<>Several prior studies have shown that lactic acid drives M2 gene expression (i.e., IL-4-induced M2 macrophage-associated genes) to promote tumor growth and progression. However, how lactic acid suppresses macrophage pro-inflammatory response (i.e., M1 polarization) is largely unknown.

<>Here, we provide evidence for a mechanism by which lactic acid exerts M2-gene-independent inhibitory effect on M1 macrophages and suggest that lactic acid acts as a primary fuel source for TCA cycle metabolism to promote histone H3K27 acetylation, which allows the expression of gene program including Nr4a1 that, in turn, inhibits macrophage pro-inflammatory response."[77.B]

The Brain

Neurons are nerve cells that store memories, memory is traditionally considered to be "patterns" of neuronal activity, or patterns of neuronal network activation, but I do not agree with this scientifically vague explanation [See: Engrams].
Neurogenesis is the formation of new neurons , **Neuritogenesis** is the formation of new neurites (the extensions of neurons), and **Synaptogenesis** is the formation of new synapses.

A Neuron Analogy

The neuron is a tree, the branches are the neurites, the branches communicate with other trees (neurons), the branches may grow or retract depending the weather (neuritogenesis / neurotoxicity), contained on the branches are buds (Vesicles) which produce fruits, these fruits contain neurotransmitters (Serotonin, GABA, Dopamine, etc.), within the tree are micropores that control nutrient regulation (ion flow), if the nutrient intake changes in a branch the fruit will fall to the ground (releasing the neurotransmitter load of vesicles). The Sun produces solar radiation (our macronutrients) which is absorbed and transformed into glucose > ATP, which stimulates growth through interacting with DNA (biological instruction books).

Neurotrophic Factors & Brain Cell Types

Brain Derived Neurotrophic Factor (bDNF) is a protein that stimulates neurogenesis and protects neurons from cell death. Newly formed neurons facilitate long term memory storage.
Regarding bDNF's relation to myogenesis, it appears that there truly is a distinction between "Brains" and "Brawn" as bDNF directly associates with muscle function.

[A] bDNF levels in myoblasts are inversely associated with hyperplasia.

"<>In skeletal muscle, brain-derived neurotrophic factor (BDNF) has long been thought to serve as a retrograde trophic factor for innervating motor neurons throughout their lifespan. However, its localization in mature muscle fibers has remained elusive. Given the postulated roles of BDNF in skeletal muscle, we performed a series of complementary experiments aimed at defining the localization of BDNF and its transcripts in adult muscle. By reverse transcription-PCR, in situ hybridization, and

immunofluorescence, we show that BDNF, along with the receptor p75NTR, is not expressed at significant levels within mature myofibers and that it does not accumulate preferentially within subsynaptic regions of neuromuscular junctions.
<>Interestingly, expression of BDNF correlated with that of Pax3, a marker of muscle progenitor cells, in several different adult skeletal muscles. Additionally, BDNF was expressed in Pax7+ satellite cells where it colocalized with p75NTR. In complementary cell culture experiments, we detected high levels of BDNF and p75NTR in myoblasts. During myogenic differentiation, expression of BDNF became drastically reduced. Using small interfering RNA (siRNA) technology to knock down BDNF expression, we demonstrate enhanced myogenic differentiation of myoblasts. This accelerated rate of myogenic differentiation seen in myoblasts expressing BDNF siRNA was normalized by administration of recombinant BDNF.
<>Collectively, these findings show that BDNF plays an important regulatory function during myogenic differentiation. In addition, the expression of BDNF in satellite cells is coherent with the notion that BDNF serves a key role in maintaining the population of muscle progenitors in adult muscle."[77.1]

[B] Astoundingly, muscle bDNF expression suppresses Neuromuscular Junction growth. This is relevant because bDNF release is systemic, and thus can be found in our serum. bDNF is then to be considered a negative modulator of muscle power and explosivity. [See: Micro-Essays: Mental Illness & Muscle Force Generation: Pg. 968]

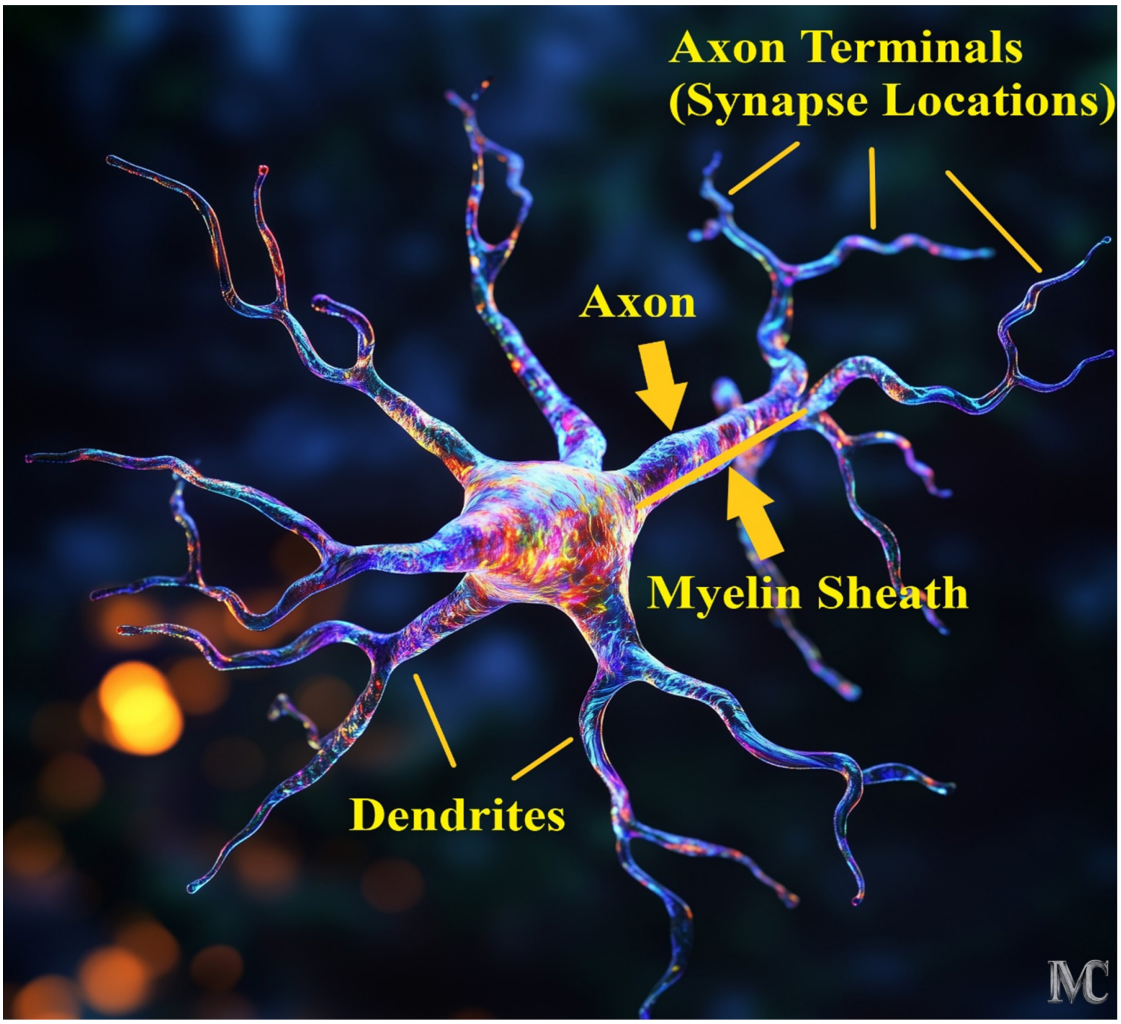
"<>The development of neuromuscular junction (NMJ) is initiated by motor axon's contact with the skeletal muscle cell that is followed by synaptic maturation. Previous studies showed that brain-derived neurotrophic factor (BDNF) enhanced motoneurons' survival and growth but significantly inhibited synaptogenesis.
<>Here, we report that chronic application of BDNF resulted in inhibition in the maturation process both physiologically and morphologically. The response to BDNF was mediated by its cognate receptor TrkB as the effects were abolished by Trk receptor inhibitor K252a. Protein kinase A (PKA) inhibitor reversed the effects of BDNF in inhibiting NMJ maturation.
<>These results indicate that BDNF suppresses NMJ maturation through cAMP-PKA signaling pathway. Together with the previous studies, these results suggest that BDNF suppresses NMJ formation and maturation despite its effects in enhancing neuronal survival and growth"[77.2]

Nerve Growth Factor (NGF) is a protein that is associated with **Neuritogenesis** i.e. The elongation of **Neurites**, which are the branches of neurons that transform into either **Axons** or **Dendrites**, making them essential for all forms of complex intelligence.
Extracellular Signal Regulated Kinase 1/2 (ERK1/2) & **Nerve Growth Factor (NGF)** are the two primary proteins that stimulate neuritogenesis.

Axons & **Dendrites** are the electrical conduits between Neurons, allowing the transmission of information & therefore activation of Neurons (Memories). **Axons**

produce **Action Potentials**, which are the signals that activate other Neurons in the brain, and they contain **Synapses** at Axon Terminals, which are the end points of Axons. **Dendrites** serve the primary function of **Backpropagation**, a process that occurs when an "echo" is formed at the beginning of an Axonal body after it has created and transmitted an Action Potential *backpropagates* through the dendritic tree, thereby allowing for *Error*-correction during complex memory formation and maintenance.

There is no doubt that recreational drug abuse leads to disruptions in backpropagation, as evidenced by the behavioral inflexibility drug abusers display, most especially the errored memories that develop after the administration of dopaminergic neurotoxins and the administration of chronic dosages of THC. As modern societies continue to experience progressive psychological regression due to neurotoxicity, and brain wave pattern disruption, owing to the abuse of Recreational Drugs, most predominately in combinatory use, the future of intellectuality seems relatively bleak.



A Backpropagation Analogy

A king consults with his councilors (dendrites) and formulates a treatise based upon his initial ideas (initial memories), he then sends an emissary (Action Potential) from his kingdoms gates (Axon Hillock) along a trail (Axon body) carrying an important treatise to a neighboring kingdom (Neighboring Neuron). When the emissary reaches the border crossing (Synapse) of his kingdom and the neighboring kingdoms' he crosses over, after reaching the new kingdom, if the treatise he was carrying is agreed with he will become part of the new kingdom, but if the treatise is rebuked, he will send a messenger bird (Backpropagation Signal) to his kingdom to notify the king of this information. After the king receives this signal he will consult with his councilors again and either remove some, add new ones, or reprimand the current ones, and after discussion and debate (memory modification) send a new emissary with a new treatise (Synaptic Plasticity: Learning) to the neighboring kingdom.

Oligodendrocytes are necessary for the formation of **Myelin**, which are the vital protective "sheaths" of neurons, specifically axons. They not only protect neurons from exterior damage such as from exposure to toxins or pathogens, but they also accelerate neural transmission through a phenomenon referred to as Saltatory Conduction. Myelin sheaths are composed of many "Nodes of Ranvier", which act electrical sinks to draw in generated action potentials, where these action potentials jump from one node to another rapidly accelerating their travel on their way to the Synapses.

Microglia are neuronal cells that respond to stress, either physical or psychological, and release inflammatory factors such as IL-6, and TNF-a. Most importantly they form phagosomes and are responsible for phagocytosis. During natural aging, or pathological aging, brain Microglia increase their production of inflammatory factors, thus increasing the risk for the development of progressive neurodegenerative conditions, such as Alzheimer's disease[77.3]. Females tend to have more active and primed Microglia, which is exacerbated following estrogen loss[77.4].

Strangely, long-term stress exposure results in a long lasting change in brain Microglia to an inflammatory phenotype, and they only revert to their previous phenotype after nearly a month, thus explaining how psychological stress promotes neuroinflammation, and how recurrent psychological stress stimulates accelerating neurotoxicity:

"<>It is of importance that chronic stress does not only prime microglia for following LPS stimulation but also for subsequent acute stress exposure, indicating that the microglia response to acute stress might resemble their responses to immune stimulation by LPS. While 1 session of social defeat (acute stress) did not increase the expression of proinflammatory mediators in microglia of naïve mice, it increased the expression of proinflammatory mediators in mice subjected to CSD 24 days earlier. This priming by CSD stress is also reflected in the behavior of the animals because acute stress was only sufficient to increase anxiety and social avoidance in mice that had been previously subjected to CSD.
<>To prove that microglia are involved in the increased susceptibility of CSD mice to acute stress, microglia were depleted using an inhibitor of the colony-stimulating factor 1

receptor (CSF1R), which microglia require for survival. This experiment showed that CSD mice were only more susceptible to acute defeat than unstressed controls when microglia were present during the acute defeat session; the priming effect of chronic stress on the susceptibility to anxiety was erased in mice lacking microglia during the acute defeat.
<>Surprisingly, the priming effect of chronic stress was observed in mice lacking microglia during the CSD itself. In mice lacking microglia during the CSD, but not during the acute defeat (because of repopulation), the acute defeat was sufficient to induce anxiety. Certainly, this rather unexpected observation needs to be further confirmed, ideally also by assessing anxious behavior in more than 1 test.
<>Nevertheless, these findings raise the following questions: (1) How is stress sensed in the absence of microglia? (2) Which persistent changes apart from microglial activation occur in the brain after exposure to chronic stress? (3) How can these changes induce a stress-sensitized microglia state once the microglia repopulate? and (4) Is it possible that residual microglia remaining after depletion can transfer the stress-sensitized phenotype to the cells they give rise to during repopulation? <>Intriguingly, this observation that microglia are primed by CSD stress although they were depleted was also made in a second study. Microglia were depleted with a CSF1R inhibitor during the CSD and allowed to repopulate after the last defeat session. Even without a subsequent acute stressor, microglia repopulation alone was sufficient to induce anxiety and social avoidance, while behavioral disturbances were absent in animals in which CSF1R inhibitor administration was continued after CSD had ended.
<>This study therefore further supports the notion that either the microglia that survived the depletion or a surrounding CNS component was altered by CSD stress in a way that enabled them to reprogram the repopulating microglia. Alternatively, it is possible that the process of microglial depletion itself, which is associated with a cytokine storm, induces changes in the CNS that then reprogram the repopulating microglia, leading to a hypersensitization of the CNS to stress."[77.4.1]

Synapses are the information-electrical conduits & information-electrical barriers between our Neurons that release **Neurotransmitters** by way of **Dense Core Vesicles** (located primarily in dendrites) and **Synaptic Vesicles** after ion channel opening. They are generally found at the end portions of Axons, where they allow electrical signals to flow between neurons.

During maturity, Synapses are progressively destroyed to form and facilitate behaviors, to refine a personality through faster transmission and signaling in the brain, this is an essential process in neurodevelopment that if not present would hypothetically cause a human being to be intellectually impaired (prone to sensory overload), clumsy, and confused by simple ideas, and they would be prone to delusional thinking due to too many patterns of thought being activated simultaneously (See: Sleep):

"<>At birth, an infant's brain is packed with roughly 100 billion neurons—some 15% more than it will have as an adult. As we learn and grow, our experiences strengthen the circuits that prove most relevant while the others weaken and fade.

<>Nerve cells in the cerebellum called purkinje cells (blue) are among the brain cells that undergo synaptic pruning as we age. Researchers are starting to recognize how pruning gone awry in children and teenagers could lay the foundation for neurological disorders. Image credit: Science Source/NIGMS/Yinghua Ma/Timothy Vartanian/Cornell University.
<> “One extreme view of this would be that you start out wired up for every possible contingency,” says Jeff Lichtman, a neuroscientist at Harvard University in Cambridge, MA. Over time, a large percentage of those wires are permanently disconnected, says Lichtman. “What you're left with is a narrower nervous system,” he explains. “But it’s tuned exactly to the world you found yourself in.”
<>The process of elimination is key to forming a healthy, adaptive brain. Researchers have documented waves of neuronal cell death and the dramatic reduction of neurons’ connecting axon fibers early in neural development. But synapses, the fixed points where one cell’s axon exchanges signals with another cell, continue to be selectively removed at least through adolescence in humans, refining a coarse neural map into mature circuits.
<>With improved imaging techniques and molecular tools, researchers are now exploring why synaptic pruning—the targeted elimination of functional synapses—happens and how it works. The amount and timing of neural activity are central to determining which synapses get reinforced and retained, and which get weaker—which flags them for destruction. Elements of the immune system appear to be essential to carrying out the elimination process. But researchers are also coming to recognize how pruning gone awry in children and teenagers could lay the foundation for neurological disorders, such as schizophrenia or autism. One possibility is that these are diseases of the wiring diagram—what Lichtman terms “connectopathies.” It may also be the case that some of the same pruning mechanisms that normally help refine brain wiring early in life contribute to later pathological synapse loss in dementia and other neurodegenerative disorders. If so, the pruning machinery could be a therapeutic target.”[77.4.2]

A Synapse Analogy

Think of the palms of your hands nearly touching as two different neurons in communication, the small gap between the palms of your hands is called the **Synaptic Cleft**, within each palm is a magnetic field where neurochemicals are secreted, these neurochemicals either activate (excite) or deactivate (inhibit) synapses. If these magnetic fields are strengthened through certain excitatory neurochemicals (Glutamate, Dopamine, Serotonin, bDNF, NGF) it is termed Long Term Potentiation, and if they are weakened through certain inhibitory neurochemicals (GABA, Adenosine, Endocannabinoids) it is termed Long Term Depression. Long Term Potentiation is required for most forms of cognition, such as memory acquisition (long term memory formation), and long term memory retrieval, whereas Long Term Depression also contributes to long term memory formation but suppresses memory acquisition.

Note: The discovery of Synapses was possibly pioneered by Sigmund Freud who referred to them as “Contact Barriers” in his pivotal and often unrecognized work Project for a

Scientific Psychology. He posited that synapses control the activation of memories (neurons) [Search: Psychological Repression].

Neurotrophic Factors, Neuropeptides, & Neurotransmitters are secreted from "**Dense-core Vesicles (DcV)**", contained within Axons & Dendrites. Think of a Neuron as being a Tree, and the Branches are the Neurites, and contained within the Neurites are Dense-core Vesicles, with the fruit grown therein being neurochemicals.

cAMP response element-binding protein (CREB) is protein that is essential for **Long Term Potentiation** (**LTP)**, alongside **NMDA Receptors**.

The **Nicotinic Acetylcholine Receptors (nAChRs)** are associated with working memory, that is to say short term memory, and also visual acuity.[77.5]

The **Muscarinic Acetylcholine Receptors (mAChRs)** are associated with long term memory, and variegated physiological processes such as heart rate, digestion and vasoreactivity.[77.6]

Neuropeptides such as **Neuropeptide Y (NPY) & Neuropeptide S (NPS)** are associated with the aforementioned neurotrophic factors, and function singularly as neurogenesis enhancers.

Neurogenesis has paradoxical roles in anxiety & depression. In the majority of scenarios, it is beneficial to promote Neurogenesis, especially in cases involving stress-induced or chemical-induced neurodegeneration. Conversely, if Neurogenesis is unchecked it promotes anxiety. Anxiety is the accumulation of electrical energy (excitation) in the brain, whereas depression in current scientific terms is best characterized by a low level of bDNF, which nearly always correlates with ongoing neurodegenerative processes.

Neurotransmitters are chemicals that change synaptic strength & promote neurogenesis. To name the primary neurotransmitters & explain them in a simplified way: There is **Dopamine** which is the On-Off switch for behaviors, reward learning, & muscle contraction, **Serotonin** which is the On-Off switch for strategy switching & fear learning (Serotonin decreases strategy switching and fear learning), **Norepinephrine** which is the On-Off switch for wakefulness & muscle contraction, **GABA** which is the motor memory facilitator, chief inhibitory chemical (anticonvulsant), & chief "creativity stimulator" by way of reducing cathected (concentrated with energy) neurons, thereby facilitating the activation of uncathected (unconscious) neurons, & finally **Acetylcholine** which plays a large role in memory consolidation (through interaction with estrogen receptors) & muscle contraction.

Chronic concentrations or chronic depletion of these neurotransmitters drastically changes behavior due to neurotoxicity. Personalities will one day be quantified by neurotransmitter concentrations, which will be a much more accurate representation of personality than the Myer-Briggs Type indicator.

A chronically elevated dopamine level in the brain is the most neurotoxic neurotransmitter scenario, because of the sleep deprivation that results, not merely because of direct neurotoxicity to our neurons mitochondria. Serotonin Receptors when acutely stimulated by SSRI's substantially promote neurogenesis, but they desensitize quite rapidly, making SSRI's a bad long-term *strategy*. GABA Receptors are paradoxical in effect, extended-chronic stimulation of them exerts a proconvulsant / anxiogenic effect.

It is interesting to note that a Testosterone breakdown product that occurs in the brain is a GABAA Receptor agonist, making Testosterone use possibly addictive, and therapeutic at the same time, similarly to Benzodiazepines[77.7].

The **Dopamine-1 (D1)** and **Dopamine-2 (D2)** Receptors are of great importance, as the former is necessary for working memory[A], and the latter is inversely associated with obesity[B].

[A] "<>In both humans and mice, performance on tests of intelligence or general cognitive ability (GCA) is related to dopamine D1 receptor-mediated activity in the prelimbic cortex, and levels of DRD1 mRNA predict the GCA of mice. Here we assessed the turnover rate of D1 receptors as well as the expression level of the D1 chaperone protein (DRiP78) in the medial PPC (mPFC) of mice to determine whether rate of receptor turnover was associated with variations in the GCA of genetically heterogeneous mice. Following assessment of GCA (aggregate performance on four diverse learning tests) mice were administered an irreversible dopamine receptor antagonist (EEDQ), after which the density of new D1 receptors were quantified. GCA was positively correlated with both the rate of D1 receptor recovery and levels of DRiP78.
<>Additionally, the density of D1 receptors was observed to increase within 60 min (or less) in response to intense demands on working memory, suggesting that a pool of immature receptors was available to accommodate high cognitive loads. These results provide evidence that innate general cognitive abilities are related to D1 receptor turnover rates in the prefrontal cortex, and that an intracellular pool of immature D1 receptors are available to accommodate cognitive demands."[77.8]

[B] "<>Background: The cerebral mechanisms underlying the behaviours that lead to pathological overeating and obesity are poorly understood. Dopamine, a neurotransmitter that modulates rewarding properties of food, is likely to be involved. To test the hypothesis that obese individuals have abnormalities in brain dopamine activity we measured the availability of dopamine D2 receptors in brain.
<>Methods: Brain dopamine D2 receptor availability was measured with positron emission tomography (PET) and [C-11]raclopride (a radioligand for the dopamine D2 receptor). Bmax/Kd (ratio of the distribution volumes in striatum to that in cerebellum minus 1) was used as a measure of dopamine D2 receptor availability. Brain glucose metabolism was also assessed with 2-deoxy-2[18F]fluoro-D-glucose (FDG).
<>Findings: Striatal dopamine D2 receptor availability was significantly lower in the ten obese individuals (2.47 [SD 0.36]) than in controls (2.99 [0.41]; p < or = 0.0075). In the obese individuals body mass index (BMI) correlated negatively with the measures of D2

receptors (r=0.84; p < or = 0.002); the individuals with the lowest D2 values had the largest BMI. By contrast, neither whole brain nor striatal metabolism differed between obese individuals and controls, indicating that striatal reductions in D2 receptors were not due to a systematic reduction in radiotracer delivery.
<>Interpretation: The availability of dopamine D2 receptor was decreased in obese individuals in proportion to their BMI. Dopamine modulates motivation and reward circuits and hence dopamine deficiency in obese individuals may perpetuate pathological eating as a means to compensate for decreased activation of these circuits. Strategies aimed at improving dopamine function may be beneficial in the treatment of obese individuals."[77.9]

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid Receptor (AMPA receptors) & **N-methyl-D-aspartate Receptor (NMDA receptors)** are the "Intelligence Receptors" (Glutamate Receptors), essential for memory encoding (acquisition), memory retrieval, and long-term memory storage through promoting **Long Term Potentiation** (LTP: Memory consolidation, long term memory storage, and long-term memory maintenance), which simply explained promotes increased communication between neurons, and this is due to an increase in synaptic strength (synaptic communication, or synapse structure). Memories are therefore
patterns of neural activity. Both LTP and LTD are forms of synaptic plasticity.
AMPA receptors are necessary for memory retrieval, whereas NMDA receptors are necessary for consolidation, and both of these receptors are required for the optimal functioning of working memory.[77.10]
Sadly, chronic activation of either the AMPArs or NMDArs causes **Excitotoxicity** (severe neuronal damage by way of mitochondrial toxicity through Ca2+), which is a phenomenon that is associated primarily with Alcohol withdrawal (NR2B Receptor hyperactivation). **Long-Term Depression (LTD)** is the opposite of LTP in that it dampens synaptic signaling, and although this reduces memory acquisition, it promotes memory consolidation:

"<>We report on findings that support that whereas LTP serves to acquire the general scheme of a spatial representation, LTD enables retention of content details. We argue that LTD contributes to learning by engaging in a functional interplay with LTP, rather than serving as its simple counterpart, or negator. We propose that similar spatial experiences that share elements of neuronal representations can be modified by means of LTD to enable pattern separation. Therewith, LTD plays a crucial role in the disambiguation of similar spatial representations and the prevention of generalization."[77.11]

Sigmund Freud explained the concept of LTP in Project for a Scientific Psychology:

"<>Long-term potentiation (LTP) of synaptic transmission is considered a reliable cellular model of several forms of learning and memory. Described for the first time in 1973, this synaptic phenomenon consists in the enduring facilitation of the

communication between two neurons in response to the sustained activation of the synapses by which they are interconnected. In a book of 1895 entitled Project for a Scientific Psychology, Sigmund Freud theorized about the possibility of representing memory at the synaptic level as "a permanent alteration following an event" and anticipated several crucial physiological properties of LTP."[78]

[A] Serotonin's effect on Strategy Switching is quite strange, but sensible. Too much of this neurotransmitter will make one "content" i.e. unable to change their behavior.
"<>Recent experiments indicate that blockade of serotonin (5-HT) 2A and 2C receptors have differential effects on reversal learning. The present experiments investigated the effects of the 5-HT(2A) receptor antagonist, ketanserin and 5-HT(2C) receptor antagonist, SB242084 on acquisition and strategy-switching in a visual cue-response paradigm. Long-Evans rats were trained in a cross-maze to enter an arm based on color (visual cue version) or a specific turn response (response version).
<>Systemic treatment with ketanserin did not affect initial learning of a visual cue or response discrimination, but ketanserin at 0.5 mg/kg significantly enhanced a switch between visual cue and response strategies. Ketanserin facilitated strategy-switching by inhibiting responses to a previously relevant strategy without affecting choices to never-reinforced strategies. Treatment with SB242084 (0.5, 1.0 or 2.0 mg/kg) did not affect acquisition of a visual cue or response discrimination. SB242084 treatment also did not affect strategy-switching.
<>The present findings suggest that blockade of 5-HT(2A), but not 5-HT(2C), receptors enhance strategy switching."[79]

[B] Serotonin's Effect On 5-HTP Receptor Desensitization.

"<>Prior exposure of SH-SY5Y/5-HT2C cells to 5-HT (1 microM/15 min) caused a significant decrease in the 5-HT-stimulated peak in Ins(1,4,5)P3 levels whereas no such change occurred in SH-SY5Y/5-HT2A cells following exposure to 10 microM 5-HT for 15 min. 6 These results indicate that the human 5-HT2A and 5-HT2C receptors both exhibit desensitization at the level of inositol phosphate formation when expressed in the same cellular environment, with the 5-HT2C receptor being more sensitive to 5-HT-mediated desensitization than the 5-HT2A receptor."[80]

[C] Dopamine is neurotoxic in high concentrations through Mitochondrial toxicity.

"<>The catechol moiety, but not the amine group, of dopamine is essential for complex I inhibition, as is indicated by comparing the inhibitory potential of functionally and structurally dopamine-related compounds. In line with the latter is the finding that chelatable FeCl2 prevented dopamine-induced inhibition of complex I. Monoamine oxidase A and B inhibitors, as well as the antioxidant butylated hydroxytoluene (BHT), did not prevent dopamine-induced inhibition, suggesting that dopamine oxidation was not involved in this process.

<>The present study suggests that dopamine toxicity involves, or is initiated by, its interaction with the mitochondrial oxidative phosphorylation system.
<>We further hypothesize that this interaction between dopamine and mitochondria is associated with mitochondrial dysfunction observed in dopamine-related neuropsychiatric disorders, such as schizophrenia and Parkinson's disease."[81]

[D] Norepinephrine reduces sleep quality.
"<>Sleep and wakefulness are instinctive behaviours that are present across the animal species. Rapid eye movement (REM) sleep is a unique biological phenomenon expressed during sleep. It evolved about 300 million years ago and is noticed in the more evolved animal species. Although it has been objectively identified in its present characteristic form about half a century ago, the mechanics of how REM is generated, and what happens upon its loss are not known. Nevertheless, extensive research has shown that norepinephrine plays a crucial role in its regulation. The present knowledge that has been reviewed in this manuscript suggests that neurons in the brain stem are responsible for controlling this state and presence of excess norepinephrine in the brain does not allow its generation.
<>Furthermore, REM sleep loss increases levels of norepinephrine in the brain that affects several factors including an increase in Na-K ATPase activity. It has been argued that such increased norepinephrine is ultimately responsible for REM sleep deprivation, associated disturbances in at least some of the physiological conditions leading to alteration in behavioral expression and settling into pathological conditions."[82]

[E] Acetylcholine promotes memory through Estrogenic upregulation of NMDA Receptors.

"<>Elevated levels of circulating estrogen in female rat's result in increased spine and synapse density and parallel increases in NMDA receptor binding in area CA1 of the hippocampus. Estrogen also influences cholinergic neurochemistry in the basal forebrain and hippocampus. The objectives of the present study were to determine the role of acetylcholine in the estrogen-induced increase in NMDA receptor binding in CA1 of the hippocampus and to investigate the relationship between increased NMDA receptor binding in CA1 and performance on a task of working memory.
<>In the current experiments, elevating endogenous levels of acetylcholine in ovariectomized rats by 3 d of continuous administration of physostigmine, an acetylcholinesterase inhibitor, increased NMDA receptor binding in CA1 as measured by quantitative autoradiography. This increase was comparable with the increase in NMDA receptor binding induced by injections of estradiol benzoate 72 and 48 hr before death.
<>Additionally, the administration of 5,11-dihydro-8-chloro-11-[[4-[3-[(2,2-dimethyl-1-oxopentyl)ethylamino]propyl]-1-piperidinyl]acetyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one (BIBN 99), an M2 receptor antagonist, blocked the ability of both estrogen and physostigmine to increase NMDA receptor binding. The regimen of estradiol replacement that was demonstrated to increase NMDA receptor binding in CA1 of

ovariectomized rats also improved arm-choice accuracy in a working memory task in an eight-arm radial maze.
<>The estrogen-induced improvement in working memory performance was blocked by BIBN 99, which also blocked the increase in NMDA receptor binding. These results indicate that acetylcholine acts at M2 muscarinic receptors to mediate the estrogen-induced increase in NMDA receptor binding in CA1 of the hippocampus as well as the associated improvement in working memory."[83]

[F] Hand dominance plays a significant role in intelligence due to differential hemisphere activation. Right handed motor movements activates the left hemisphere of the brain (analytic thinking), whereas left handed motor movements activate the right hemisphere of the brain (creative thinking). It appears that left handedness results in greater brain symmetry than right handedness, meaning that left handed individuals are liable to have higher intelligences, including creative potential, as evidenced by the differences in "small-world properties" (predicted mathematical brain connectivity), which is likely due to the enhanced growth of corpus callosum tissue in left handed people.
Interestingly, anyone can become left handed, if only for a day, as it is not terribly difficult to consciously and purposefully change your dominant hand during daily tasks, although writing may be difficult, it may very well grow your corpus callosum.

"<>Previous behavioral and scanning studies have suggested that handedness is associated with differences in brain morphology as well as in anatomical and functional lateralization. However, little is known about the topological organization of the white matter (WM) structural networks related to handedness.
<>We employed diffusion tensor imaging tractography to investigate handedness- and hemisphere-related differences in the topological organization of the human cortical anatomical network. After constructing left hemispheric/right hemispheric weighted structural networks in 32 right-handed and 24 left-handed healthy individuals, we analyzed the networks by graph theoretic analysis.
<>We found that both the right and left hemispheric WM structural networks in the two groups possessed small-world attributes (high local clustering and short paths between nodes), findings which are consistent with recent results from whole-brain structural networks. In addition, the right hemisphere tended to be more efficient than the left hemisphere, suggesting a high efficiency of general information processing in the right hemisphere.
<>Finally, we found that the right-handed subjects had significant asymmetries in small-world properties (normalized clustering coefficient γ, normalized path length λ, and small-worldness σ), while left-handed subjects had fewer asymmetries. Our findings from large-scale brain networks aid in understanding the structural substrates underlying handedness-related and hemisphere-related differences in cognition and behavior."[83.0.1]

[F2] The corpus callosum, the part of the brain that connects the hemispheres, is larger in left handed people by an astounding "11" percent.

"<>The size of the midsagittal area of the human corpus callosum obtained from postmortem measurement varied with tested hand preference. The corpus callosum, the main fiber tract connecting the two cerebral hemispheres, was larger by about 0.75 square centimeter, or 11 percent, in left-handed and ambidextrous people than in those with consistent right-hand preference. The difference was present in both the anterior and posterior halves, but not in the region of the splenium itself. This callosal morphology, which varied with hand preference, may also be related to individual differences in the pattern of hemispheric functional specialization.
<>The greater bihemispheric representation of cognitive functions in left- and mixed-handers may be associated with greater anatomical connection between the hemispheres. The naturally occurring regressive events in neurogenesis, such as neuronal cell death and axonal elimination, may be factors in the individual differences in brain morphology and in functional lateralization. Specifically, right-handers may be those with more extensive early elimination of neural components."[83.0.2]

[F3] Strangely, ADHD appears to be associated with left handedness, which may at first glance seem contradictory to the above research, but this could be explained by the inefficient nature of public schools, where the stimuli that is offered to gifted developing minds is too mundane to stimulate and draw their attention away from artistic expression. Furthermore, if left handedness is associated with some form of hyperactivity, or impulsivity, but enhanced creativity, than we can suggest that right handedness, being an analytically dominant laterization, is associated with reduced creativity, and therefore that whatever hand dominance a child has, if they show developmental issues, they should be forced in school to write with their non-dominant hand, to rectify any hemispheric differences, and promote their intelligence. This would be a novel way to help gifted children reach their potential, not through prescription use, but through motor actuation.

"<>Background: Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder. Continuous performance Tests (CPTs) aid the diagnosis. Handedness is linked to disabilities.
<>Objectives: 1-To study the association between handedness and ADHD; 2-To verify the usefulness of the CPT in school settings; 3-To exam the relationship between handedness and CPT performance.
<>Method: Each child was classified as right-consistent, left-consistent, or non-consistent. From the sample, 171 controls and 68 ADHDs fulfilled the inclusion criteria. The effect of handedness on the CPT was studied using a paired-sample that matched handedness by age, grade, gender, and ADHD.
<>Results: Left-handed students had a probability of suffering from ADHD 2.88 greater than right-handers. ANOVAs on standardized scores indicated that the ADHD students exhibited higher number of errors and higher variability of reaction times as compared to the controls. Discriminant analysis indicated that these CPT parameters could discriminate ADHD from controls. Repeated ANOVAs showed a significant effect of

handedness on commission errors (CE) because left-handers made more CEs than right-handers.
<>Conclusions: 1-The association between ADHD and handedness reflects that left-handers are less lateralized and have decreased interhemispheric connections; 2-The CPT can be used to measure different attention domains in school settings; 3- Left-handers have problems in the impulsive/hyperactivity domain."[83.0.3]

The **Cannabinoid Receptors 1-2 (CB1 / CB2)** are associated with social defeat stress, threat processing, and cellular immunity.
[See: Common Recreational Chemicals: THC]

Neurodegeneration

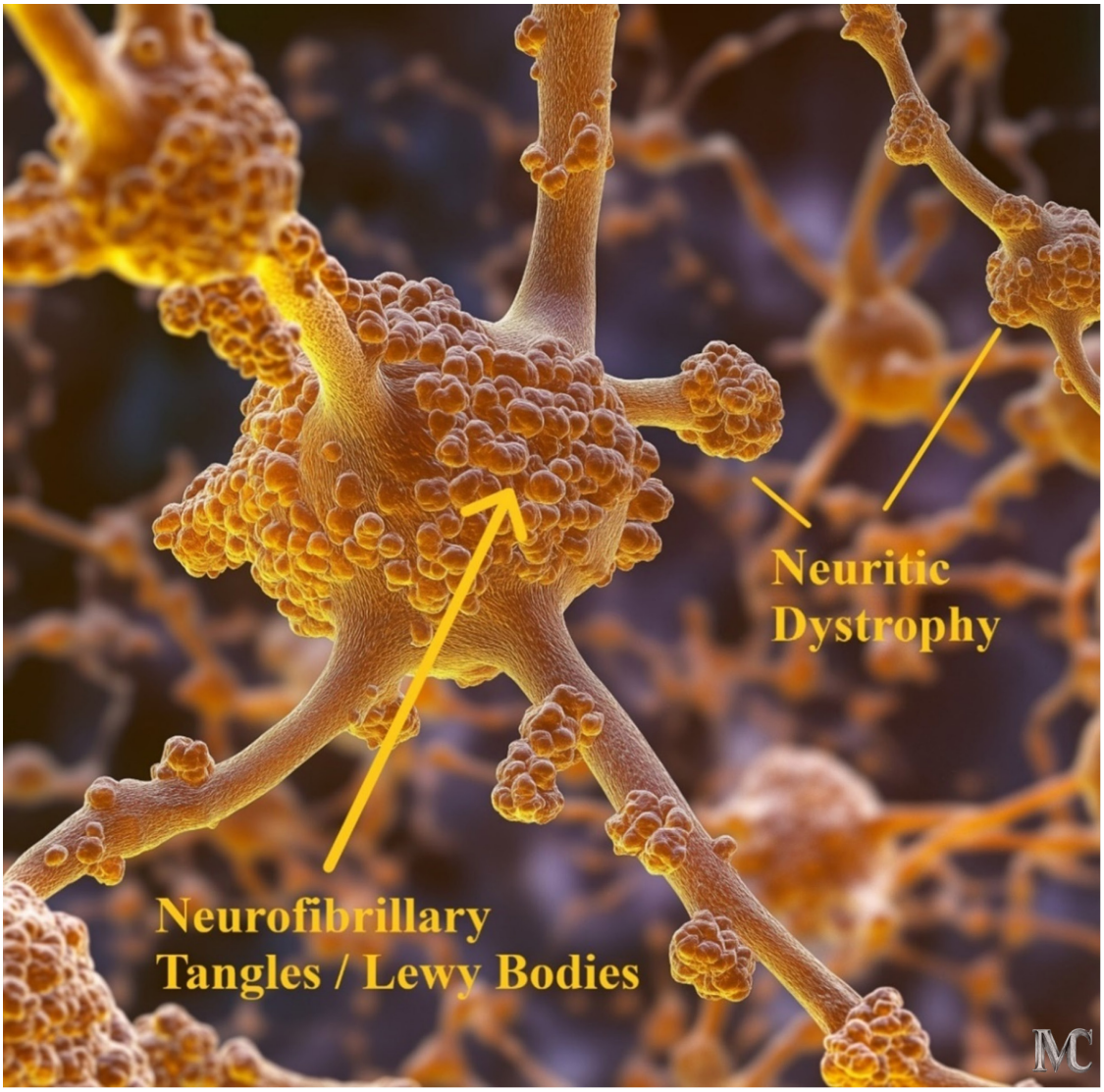
The most common forms of **Dementia** are caused by the excess deposition of **Beta-Amyloid** (Alzheimer's Disease), **Tau** (Neurofibrillary Tangles: Tauopathy), **Alpha-Synuclein** (Lewy Body Dementia), & the often unrecognized **Ceramide** in the human brain. These forms of neurological molecular waste form in the brain through bad dietary choices (Examples: Fructose, Palmitic acid), drug use, genetics, & sleep deprivation. Hyperphosphorylated (hyperactive) Tau Protein in the brain is associated with Dementias, but also brain aging in general, as Neurofibrillary Tangles are found in elderly but healthy brains and used as a potential marker of neurodegeneration.
It is safe to say without adding research that nutrient deficiencies play a major role in the development of aging-induced neurocognitive decline, as the diets of our elders are often poisonous (high carbohydrate, high non-essential fat, low protein, low essential fat, et cetera).

Beta-Amyloid is the active and toxic protein that forms Amyloid Plaques, alongside other molecules that accumulate in the brain such as Tau, and Alpha-Synuclein. It is produced naturally in the brain throughout life, but when the brain loses its ability to "clean" itself of these proteins by way of Glymphatic Function, the neurodegenerative process and progression towards Dementias is facilitated.
Tau is a protein that controls **Microtubule** formation and function, Microtubules are contained within Axons and Dendrites and are to be considered the "railways" of cargo transfer between Neurons, carrying proteins and vesicles.
Alpha-Synuclein regulates neurotransmitter release, but when it accumulates it formed Lewy Bodies, which are similar to Amyloids, and accumulate in the brain, resulting in the development of Dementia.

I believe certain forms of Dementia are a defense mechanism the brain takes to combat frequent social defeat stress, loneliness, or a lack of environmental enrichment. Although this may seem to be an insane hypothesis, psychological experiences play a far greater role than many are willing to admit to in what regards neurodevelopment, and neurodegeneration. It is often quoted that "*religion is the opiate of the masses*", but that's

only a simplification and misrepresentation of the truth, for sociality in all its forms is the opiate the masses. There is no doubt that the social isolation and severe lack of environmental enrichment that dementia patients experience only exacerbates their mental deterioration. I am quite certain that loneliness can be described as the primary progressive mechanical process of neurodegeneration due to psychological circumstances as evidenced by the study below:

"<>Importance: Emotional and behavioral symptoms in cognitively normal older people may be direct manifestations of Alzheimer disease (AD) pathophysiology at the preclinical stage, prior to the onset of mild cognitive impairment. Loneliness is a perceived state of social and emotional isolation that has been associated with cognitive and functional decline and an increased risk of incident AD dementia. We hypothesized that loneliness might occur in association with elevated cortical amyloid burden, an in vivo research biomarker of AD.
<>Objective: To determine whether cortical amyloid burden is associated with greater loneliness in cognitively normal older adults.
<>Design, setting, and participants: Cross-sectional analyses using data from the Harvard Aging Brain Study of 79 cognitively normal, community-dwelling participants. A continuous, aggregate measure of cortical amyloid burden, determined by Pittsburgh Compound B-positron emission tomography (PiB-PET), was examined in association with loneliness in linear regression models adjusting for age, sex, apolipoprotein E ε4 (APOEε4), socioeconomic status, depression, anxiety, and social network (without and with the interaction of amyloid and APOEε4). We also quantified the association of high amyloid burden (amyloid-positive group) to loneliness (lonely group) using logistic regression, controlling for the same covariates, with the amyloid-positive group and the lonely group, each composing 32% of the sample (n = 25).
<>Main outcomes and measures: Loneliness, as determined by the 3-item UCLA Loneliness Scale (possible range, 3-12, with higher score indicating greater loneliness).
<>Results: The 79 participants included 43 women and 36 men with a mean (SD) age of 76.4 (6.2) years. Mean (SD) cortical amyloid burden via PiB-PET was 1.230 (0.209), and the mean (SD) UCLA-3 loneliness score was 5.3 (1.8). Twenty-two (28%) had positive APOEε4 carrier status, and 25 (32%) were in the amyloid-positive group with cortical PiB distribution volume ratio greater than 1.2. Controlling for age, sex, APOEε4, socioeconomic status, depression, anxiety, and social network, we found that higher amyloid burden was significantly associated with greater loneliness: compared with individuals in the amyloid-negative group, those in the amyloid-positive group were 7.5-fold (95% CI, 1.7-fold to 34.0-fold) more likely to be classified as lonely than nonlonely (β = 3.3, partial r = 0.4, P = .002). Furthermore, the association of high amyloid burden and loneliness was stronger in APOEε4 carriers than in noncarriers.
<>Conclusions and relevance: We report a novel association of loneliness with cortical amyloid burden in cognitively normal older adults, suggesting that loneliness is a neuropsychiatric symptom relevant to preclinical AD. This work will inform new research into the neural underpinnings and disease mechanisms involved in loneliness and may enhance early detection and intervention research in AD."[83.0]



The accumulation of toxic protein aggregates in the human brain during aging is inevitable, as if not formed through macronutrient digestion, they are formed through drug use, or exposure to environmental toxins. The ultimate goal should be to mitigate, not stop, the formation of molecular trash in the brain, and this can be accomplished cheaply by increasing slow wave sleep duration, by engaging in higher intensity forms of cardiovascular exercise, and most importantly through decreasing your consumption of junk foods, meats, and cheeses that are loaded with Palmitic acid, which directly promote Beta-Amyloid generation in the brain:

“<>Alzheimer's disease (AD), the most common chronic and progressive neurodegenerative disorder, is characterized by extracellular deposits of amyloid β-peptides (Aβ) and intracellular deposits of hyperphosphorylated tau (phospho-tau) protein. Ceramides, the major molecules of sphingolipid metabolism and lipid second messengers, have been associated with AD progression and pathology via Aβ generation.

Enhanced levels of ceramides directly increase Aβ through stabilization of β-secretase, the key enzyme in the amyloidogenic processing of Aβ precursor protein (APP). As a positive feedback loop, the generated oligomeric and fibrillar Aβ induces a further increase in ceramide levels by activating sphingomyelinases that catalyze the catabolic breakdown of sphingomyelin to ceramide.
<>Evidence also supports important role of ceramides in neuronal apoptosis. Ceramides may initiate a cascade of biochemical alterations, which ultimately leads to neuronal death by diverse mechanisms, including depolarization and permeabilization of mitochondria, increased production of reactive oxygen species (ROS), cytochrome c release, Bcl-2 depletion, and caspase-3 activation, mainly by modulating intracellular signalling, particularly along the pathways related to Akt/PKB kinase and mitogen-activated protein kinases (MAPKs).”[83.1]

[A] Fructose [See: Fructose, Sucrose, & Advanced Glycation End Products] promotes amyloid deposition in the brain. Melatonin reverses this toxic process.

“<>Although numerous studies have demonstrated the harmful effect of excessive fructose consumption at the systemic level, there is little information on its effects in the central nervous system.
<>The purpose of the present work was to study the cellular alterations related to oxidative stress and protein quality control systems induced by a high-fructose diet in the brain of Syrian hamsters and their possible attenuation by exogenous melatonin. <>High-fructose intake induced type II diabetes together with oxidative damage, led to alterations of the unfolded protein response by activating the eIF2α branch, and impaired the macroautophagic machinery in the brain, favoring the accumulation of aggregates labeled for selective degradation and neurodegeneration markers such as β-amyloid (1-42), tau-p-S199, and tau-p-S404. Melatonin attenuated the manifestation of type II diabetes and reduced oxidative stress, deactivated eIF2α, and decreased tau-p-S404 levels in the brain of animals fed a high-fructose diet.”[83.A]

[B] High Sodium Intake increases Tau Burden, and it suppresses angiogenesis (See: Pro-Inflammation Cycle Diet), which will surely predispose a brain to physiological insult (damage).

“<>Dietary habits and vascular risk factors promote both Alzheimer's disease and cognitive impairment caused by vascular factors. Furthermore, accumulation of hyperphosphorylated tau, a microtubule-associated protein and a hallmark of Alzheimer's pathology, is also linked to vascular cognitive impairment. In mice, a salt-rich diet leads to cognitive dysfunction associated with a nitric oxide deficit in cerebral endothelial cells and cerebral hypoperfusion. Here we report that dietary salt induces hyperphosphorylation of tau followed by cognitive dysfunction in mice, and that these effects are prevented by restoring endothelial nitric oxide production. The nitric oxide deficiency reduces neuronal calpain nitrosylation and results in enzyme activation, which, in turn, leads to tau phosphorylation by activating cyclin-dependent kinase. Salt-induced

cognitive impairment is not observed in tau-null mice or in mice treated with anti-tau antibodies, despite persistent cerebral hypoperfusion and neurovascular dysfunction. <>These findings identify a causal link between dietary salt, endothelial dysfunction and tau pathology, independent of haemodynamic insufficiency. Avoidance of excessive salt intake and maintenance of vascular health may help to stave off the vascular and neurodegenerative pathologies that underlie dementia in the elderly."[83.B]

[C] Only higher intensity forms of exercise reduce Tau burden in the brain.

"<>Numerous animal studies have reported exercise reduces the accumulation of Alzheimer's disease pathology, including amyloid-β (Aβ) and tau. Furthermore, we previously reported a relationship between higher levels of physical activity (PA) and lower brain Aβ burden in a human population. The recent advent of tau positron emission tomography (PET) tracers enables us to extend our investigations into the evaluation of the relationship between PA and brain tau burden. Utilizing data from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study, we have examined the cross-sectional relationship between habitual PA and PET-quantified tau burden. Forty-three cognitively healthy older adults were categorized into low-moderate PA (LMPA; n = 16) or high PA (HPA; n = 27), based on self-reported PA levels. Tau PET imaging with the AV1451 tracer was conducted on all participants.
<>The LMPA group had significantly higher neocortical tau burden (presented as a z-score; 1.22±1.98), compared to the HPA group (z-score: - 0.28±1.18). The difference between the LMPA and HPA groups was also evident when examining regional tau burden in the temporoparietal cortex and the prefrontal cortex. Our results suggest an association between self-reported PA level and brain tau burden. Future longitudinal and interventional studies utilizing larger samples sizes are vital to further investigate the nature of the relationship between tau and PA."[83.C]

[D] Sleep is necessary for the clearance of molecular waste in the brain. When we sleep, *Cerebrospinal Fluid* flows over neurons like an ocean tide, cleansing the brain of molecular waste.

"<>Proteins linked to neurodegenerative diseases, including β-amyloid (Aβ) (8), α-synuclein, and tau, are present in the interstitial space surrounding cells of the brain. In peripheral tissue, lymph vessels return excess interstitial proteins to the general circulation for degradation in the liver. Yet despite its high metabolic rate and the fragility of neurons to toxic waste products, the brain lacks a conventional lymphatic system. Instead, cerebrospinal fluid (CSF) recirculates through the brain, interchanging with interstitial fluid (ISF) and removing interstitial proteins, including Aβ. The convective exchange of CSF and ISF is organized around the cerebral vasculature, with CSF influx around arteries, whereas ISF exits along veins. These pathways were named the glymphatic system on the basis of their dependence on astrocytic aquaporin-4 (AQP4) water channels and the adoption of functions homologous to peripheral lymphatic removal of interstitial metabolic byproducts. Deletion of AQP4 channels reduces

clearance of exogenous Aβ by 65%, suggesting that convective movement of ISF is a substantial contributor to the removal of interstitial waste products and other products of cellular activity.
<>Because of the high sensitivity of neural cells to their environment, it is essential that waste products of neural metabolism are quickly and efficiently removed from the brain interstitial space. Several degradation products of cellular activity, such as Aβ oligomers and amyloid depositions, have adverse effects on synaptic transmission and cytosolic Ca2+ concentrations and can trigger irreversible neuronal injury. The existence of a homeostatic drive for sleep—including accumulation of a "need to sleep" substance during wakefulness that dissipates during sleep—has been proposed. <>Because biological activity is inevitably linked to the production of metabolic degradation products, it is possible that sleep subserves the important function of clearing multiple potentially toxic CNS waste products. Our analysis indicates that the cortical interstitial space increases by more than 60% during sleep, resulting in efficient convective clearance of Aβ and other compounds.
<>The purpose of sleep has been the subject of numerous theories since the time of the ancient Greek philosophers. An extension of the findings reported here is that the restorative function of sleep may be due to the switching of the brain into a functional state that facilitates the clearance of degradation products of neural activity that accumulate during wakefulness."[83.D]

[E] L-Serine, when administered twice per day at a dosage of 168mg x kg, enhances the regeneration of the brain post-stroke through multiple neurotrophins, and *promotes angiogenesis* in the brain. NSC = Neural Stem Cell.

"<>In addition, the present study found that L-serine treatment elevated the expression of five nerve growth related factors: GDNF, NGF, NCAM L1, TN-C, and Nogo-A in the ischemic brain tissue of rats after pMCAO. GDNF, an important neurotrophic factor, has been demonstrated to promote the survival of many neurons, neurite outgrowth, and synaptogenesis. Duan et al. found that GDNF may improve the proliferation of endogenous NSCs in humans after cerebral ischemia. Moreover, exogenous GDNF may exert a neuroprotective effect on the brain in different experimental models of focal and global brain ischemia. NGF is also important for the survival, maintenance and regeneration of specific neuronal populations in the adult brain. Intracerebroventricular or intracerebral administration of NGF will improve neurological recovery after cerebral ischemia or traumatic brain injury. NCAM L1 has critical roles in axon outgrowth and fasciculation, neuronal migration and survival, and synaptic plasticity during nervous system development and promotes regeneration in animal models of acute and chronic injury of the adult nervous system. In addition, some studies have indicated that transplantation of embryonic stem cells that express the NCAM L1 supported the regrowth of corticospinal axons, promoted spinal cord regeneration and improved functional recovery after spinal cord injury.
<>To investigate the potential effect of L-serine treatment on microvascular proliferation, vWF+ endothelial cells were observed in the IBZ of rat cortex 5 days after pMCAO. The

total number of vWF-positive microvessels was divided by the total tissue-area to determine vascular density. Data are presented as the number of vWF-positive microvessels/mm2. L-serine treatment increased the number of vWF+ microvessels ($p<0.01$).
<>In conclusion, L-serine treatment in pMCAO rats can reduce brain injury and facilitate neurorestoration which is partly associated with the improvement of proliferation of NSCs and microvessels, reconstruction of neurovascular units and resultant neurorepair. The effects of L-serine on endogenous NSC proliferation and microvascular proliferation are partly mediated by the action of L-serine as a substrate for the production of one-carbon groups used for purine and pyrimidine synthesis and modulation of the expression of some endogenous nerve growth-related factors."[83.E]

[F] 2.5 Microns Air Particle Pollution worsens cognitive decline. [See: Air Quality]

"<>Objective: Although chronic exposure to air pollution is associated with an increased risk of dementia in normal elderlies, the effect of chronic exposure to air pollution on the rates of cognitive decline in Alzheimer's disease (AD) has not been elucidated.
<>Methods: In this longitudinal study, a total of 269 patients with mild cognitive impairment or early dementia due to AD with the evidence of brain β-amyloid deposition were followed-up for a mean period of 4 years. Five-year normalized hourly cumulative exposure value of each air pollutant, such as carbon monoxide (CO), nitrogen dioxide (NO2), sulfur dioxide (SO2), and particulate matter (PM2.5 and PM10), was computed based on nationwide air pollution database. The effects of chronic exposure to air pollution on longitudinal cognitive decline rate were evaluated using linear mixed models.
<>Results: Higher chronic exposure to SO2 was associated with a faster decline in memory score, whereas chronic exposure to CO, NO2 , and PM10 were not associated with the rate of cognitive decline. Higher chronic exposure to PM2.5 was associated with a faster decline in visuospatial score in apolipoprotein E ε4 carriers. These effects remained significant even after adjusting for potential confounders.
<>Interpretation: Our findings suggest that chronic exposure to SO2 and PM2.5 is associated with faster clinical progression in AD."[83.F]

[G] Aromatherapy (Lemon, Rosemary, Orange, & Lavender oil) breaks down amyloid proteins in the brain. The complexity of our Olfactory system is a clear reminder that we evolved from primordial shrew-like creatures and hints to the necessity of Volatile Organic Compound exposure during life for facilitation of healthy aging.

"<>Alzheimer's disease (AD) is a progressive neurodegenerative disease and is known to be the most common cause of dementia. We previously described the benefits of aromatherapy on the cognitive function of patients with AD utilizing various aromatic essential oils; however, its mechanism of action remains poorly understood. Consequently, in the present study, this mechanism was thoroughly evaluated employing a dementia mice model, specifically the senescence-accelerated mouse prone 8.

<>The mice were exposed to a mixture of lemon and rosemary oil at nighttime as well as to a mixture of lavender and orange oil in the daytime for 2 months. The cognitive function of the mice was assessed before and after treatment with the aromatic essential oils using the Y-maze test. Moreover, the brain levels of amyloid beta (Aβ), abnormally phosphorylated tau, and brain-derived neurotrophic factor (BDNF) were measured following treatment.
<>The benefits of aromatherapy on the cognitive function in mice were confirmed. It was also established that the brain levels of Aβ and abnormally phosphorylated tau were considerably lower in the aromatherapy group, while the levels of BDNF were marginally higher. These results suggest that aromatherapy employing these aromatic essential oils is beneficial for the prevention and treatment of AD."[83.G1]

[G2] Linalool, the primary chemical component of interest in Lavender oils inhibits amyloid aggregation (it inhibits the spread of amyloid-beta fibrils). Essential oils should be constantly diffused in the rooms and near the beds of all dementia patients, or an even better idea is to saturate their pillows with Essential oil blends before bed. Also, considering many Essential oil chemical components permeate through the skin to reach systemic circulation, See: TALMS.

"<>Linalool is a neuroprotective monoterpene found in essential oils from aromatic plants. Linalool's effectiveness in AD animal models has been established previously, but its mechanisms of action remain unclear. Therefore, this study aims to investigate whether linalool binds directly to the amyloid beta (Aβ) fibrils to understand it's role in preventing neurodegeneration.
<>The anti-aggregation ability of Linalool was determined using Dithiothreitol (DTT), and thermal aggregation assays followed by Thioflavin T (ThT) binding assay. AD animals were treated with Linalool, and Thioflavin T staining was used to check the binding of linalool to Aβ fibrils in rat brain tissue sections. Preliminary studies revealed the anti-aggregation potential of linalool under the thermal and chemical stimulus.
<>Further, in ThT binding assay Linalool inhibited Aβ aggregation, binding directly to Aβ fibrils. The reduced fluorescence intensity of ThT in AD brain tissues following linalool administration, highlights its neuroprotective potential as a therapeutic agent for AD."[83.G2]

[H] Oak & Chestnut contain phytochemicals called Ellagitannins, specifically Vescalagin (1) & Castalagin (2), which are capable of remodeling amyloid oligomers (molecules) into non-toxic derivatives, and more impressively, are capable of protecting live neuronal cells (SH-SY5Y cells) from amyloid-induced neurotoxicity by nearly 100% efficiency after only 24h incubation, depending on the concentration. And no, I am not suggesting consuming alcoholic drinks aged in wooden barrels. You can purchase "Wine Tannin" powder online very easily and add it to a shake (or food?). Castalagin has an LD50 (Median Lethal Dose) of 285mg / kg[83.H1].

“<>Polyphenolic compounds are able to interact with Aβ4211-14. This interaction is mainly driven by the binding of the polyphenols’ aromatic rings with the amino and sulfhydryl groups of the peptide; or directly through – stacking between the same aromatic rings and the Aβ42 aromatic aminoacidic residues (e.g. phenylalanine). Based on these studies we evaluated the capacity of two cork polyphenols, i.e. vescalagin (1) and castalagin (2) to remodel the supramolecular organization of oligomeric Aβ42 into non-cytotoxic forms. The extraction and identification of each compound was optimized and performed following a previous work.”
“<>Our data suggests that both 1 and 2 are interacting with Aβ42, remodelling its supramolecular organization and morphological presentation, reducing the concentration of oligomers. To evaluate if compounds 1 and 2 are in fact able to
reduce the Aβ42-mediated cell death we performed a cytotoxicity assay using SH-SY5Y cells. To this end, Aβ42 (in the monomeric form) was incubated with SH-SY5Y cells and their viability was quantified after 24h using standardized MTS and
Live/Dead assays.
<>When Aβ42 was added at a concentration of 25μM, there was a decrease on cell viability to ∼50%. Maintaining this concentration of Aβ42, we added different concentrations of 1 and 2 (i.e. 12.5μM, 25μM and 50μM). Cellular metabolic activity is recovered to ∼100%, after 24h for all the tested conditions. In addition, Live/Dead assay confirmed the same tendency showing that both 1 and 2 are able to rescue cell viability after 24h of incubation. Quantification of the percentage of live cells revealed that the cytotoxicity of Aβ42 resulted in less than 50% of live cells, however, 1 and 2 were able to rescue cells from death to a level similar to the control experiments, i.e. ∼100% of live cells.”
“<>Overall, our data suggests that there is a higher propensity of 1 to interact with Aβ42 when compared with 2. While being surprising, as the structural difference between 1 and 2 is only in the spatial organization of their OH group at the C1 position of the glycosidic chain, it has been already reported that this difference leads to higher reactivity, increased polarity and lower lipophilicity of 1 compared to 2. Overall, 1 is able not only to rearrange the Aβ42 secondary structure, leading to the formation of non-cytotoxic structures (without their typical antiparallel β-sheets arrangement). Taken together, the ability of 1 to modulate the Aβ42 aggregation pathway eliminating the characteristic cytotoxic oligomers is a step forward in the development of compounds with the capacity to control the trigger and/or progression of AD. Despite the higher activity of 1, it is clear that 2 is also able to interact with Aβ42 and reduce its cytotoxicity towards the neuroblastoma cell line SH-SY5Y.”[83.H2]

[I] Nerve Growth Factor “potentiates” beta-amyloid neurotoxicity.

Strangely, NGF appears to potentiate the neurotoxicity of Alzheimer’s disease, which actually makes sense when we remember that many growth factors promote the spread of cancer, such as VEGF, and TGF-b. Anabolic processes that go unchecked will always lead to deleterious consequences.

"<>The role of growth factors in the pathogenesis of Alzheimer disease is unknown. The beta-amyloid protein accumulates abnormally in the brain in Alzheimer disease and is neurotoxic to differentiated hippocampal neurons in culture. Nerve growth factor (NGF) increased the neurotoxic potency of a beta-amyloid polypeptide by a factor of approximately 100,000, which resulted in a reduction of the beta-amyloid neurotoxic EC50 from 0.1 microM to 1 pM.
<>This potentiating effect of NGF was reversed by a monoclonal antibody against NGF and was not observed for a variety of other neurotrophic growth factors. Exposure of hippocampal neurons to very low concentrations of beta amyloid alone resulted in a marked induction of immunoreactive NGF receptors.
<>Addition of NGF with beta amyloid resulted in the appearance of neurodegenerative changes in NGF receptor-positive neurons. The early and profound degeneration of hippocampal and basal forebrain cholinergic neurons that occurs in Alzheimer disease may result from a neurotoxic interaction of beta amyloid with NGF."[83.I]

[J] GSK3B contributes to Alzheimer's disease (and other Dementias) development and spread, which means Lithium use (being a GSK3B inhibitor) is an excellent preventative measure against the subtle or chronic neurodegeneration that is likely to accompany natural or pathogenic brain aging.
[See: Anti-Inflammation Cycle Supplementation: Lithium]

"<>Glycogen synthase kinase-3 (GSK-3) is a pivotal molecule in the development of Alzheimer's disease (AD). GSK-3beta is involved in the formation of paired helical filament (PHF)-tau, which is an integral component of the neurofibrillary tangle (NFT) deposits that disrupt neuronal function, and a marker of neurodegeneration in AD. GSK-3beta has exactly the same oligonucleotide sequence as tau-protein kinase I (TPKI), which was first purified from the microtubule fraction of bovine brain. <>Initially, we discovered that GSK-3beta was involved in amyloid-beta (Abeta)-induced neuronal death in rat hippocampal cultures. In the present review, we discuss our initial in vitro results and additional investigations showing that Abeta activates GSK-3beta through impairment of phosphatidylinositol-3 (PI3)/Akt signaling; that Abeta-activated GSK-3beta induces hyperphosphorylation of tau, NFT formation, neuronal death, and synaptic loss (all found in the AD brain); that GSK-3beta can induce memory deficits in vivo; and that inhibition of GSK-3alpha (an isoform of GSK-3beta) reduces Abeta production.
<>These combined results strongly suggest that GSK-3 activation is a critical step in brain aging and the cascade of detrimental events in AD, preceding both the NFT and neuronal death pathways. Therefore, therapeutics targeted to inhibiting GSK-3 may be beneficial in the treatment of this devastating disease."[83.J]

[K] Interestingly, Testosterone, by way of the Ca2+ ion channels, enhances neurite outgrowth, making Testosterone not only an anxiolytic but also a neurotrophic sex hormone. TRT Therapy is therefore extremely likely to mitigate aging-induced neurodegeneration. Furthermore, the study below is evidence for the subtle neurological advantage enhanced athletes have, for any enhancement to brain cell growth will promote

motor memory and motor pathway effectiveness, meaning that there exists both a myogenic and neurogenic disadvantage between athletes who are natural and athletes who are not.

"<>Testosterone has short- and long-term roles in regulating neuronal function. Here, we show rapid intracellular androgen receptor-independent effects of testosterone on intracellular Ca2+ in neuroblastoma cells. We identified testosterone-induced Ca2+ signals that began primarily at the neurite tip, followed by propagation towards the nucleus, which was then repeated to create an oscillatory pattern.
<>The initial transient depended upon production of inositol 1,4,5-trisphosphate [Ins(1,4,5)P3], but subsequent transients required both extracellular Ca2+ influx and Ca2+ release from intracellular stores. Inhibition of pertussis toxin-sensitive G-protein receptors or the use of siRNA for the Ins(1,4,5)P3 receptor type 1 blocked the Ca2+ response, whereas inhibition or knock-down of the intracellular androgen receptor was without effect. Cytosolic and nuclear Ca2+ were buffered with parvalbumin engineered to be targeted to the cytosol or nucleus. Cytoplasmic parvalbumin blocked Ca2+ signaling in both compartments; nuclear parvalbumin blocked only nuclear signals. Expression of a mutant parvalbumin did not modify the testosterone-induced Ca2+ signal. Neurite outgrowth in neuroblastoma cells was enhanced by the addition of testosterone. This effect was inhibited when cytosolic Ca2+ was buffered and was attenuated when parvalbumin was targeted to the nucleus.
<>Our results are consistent with a fast effect of testosterone, involving Ins(1,4,5)P3-mediated Ca2+ oscillations and support the notion that there is synergism in the pathways used for neuronal cell differentiation involving rapid non-genomic effects and the classical genomic actions of androgens."[83.K]

[L] B-Hydroxybutyrate reverses beta-amyloid accumulation through increased neuronal autophagy, thus providing increased evidence for why the Ketogenic Diet delays systemic aging and making us question why the dietary food prepared and doled out in Assisted Living homes to elderly patients with Dementia are so carbohydrate and palmitic acid rich, and so low in protein and essential nutrients when their diets should be *precisely the reverse* (depending on disease progression, insulin will exert antiapoptotic effects, but it will not prevent amyloid deposition).

"<>Loss of proteostasis is a hallmark of aging and Alzheimer disease (AD). Here, we identify β-hydroxybutyrate (βHB), a ketone body, as a regulator of protein solubility in the aging brain. βHB is a small molecule metabolite which primarily provides an oxidative substrate for ATP during hypoglycemic conditions, and also regulates other cellular processes through covalent and noncovalent protein interactions. We demonstrate βHB-induced protein insolubility across in vitro, ex vivo, and in vivo mouse systems. This activity is shared by select structurally similar metabolites, is not dependent on covalent protein modification, pH, or solute load, and is observable in mouse brain in vivo after delivery of a ketone ester.

<>Furthermore, this phenotype is selective for pathological proteins such as amyloid-β, and exogenous βHB ameliorates pathology in nematode models of amyloid-β aggregation toxicity. We have generated a comprehensive atlas of the βHB-induced protein insolublome ex vivo and in vivo using mass spectrometry proteomics, and have identified common protein domains within βHB target sequences. Finally, we show enrichment of neurodegeneration-related proteins among βHB targets and the clearance of these targets from mouse brain, likely via βHB-induced autophagy. <>Overall, these data indicate a new metabolically regulated mechanism of proteostasis relevant to aging and AD."

↓ continued

"<>The fasting metabolic state is known to be linked to proteostasis via target of rapamycin (TOR) protein kinase complex activity. TOR is activated under conditions of nutrient or energy surplus to increase translation throughput and suppress autophagy. ATP itself (but not ADP) functions as a hydrotope at physiological concentrations to maintain solubility of hydrophobic proteins that might otherwise be aggregation-prone. <>The current data implicating fasting metabolites, including R-βHB, in inducing protein insolubility to enhance degration is consistent with a broad model of cells favoring protein synthesis and stability in times of nutrient excess, and favoring repair and turnover in times of nutrient deprivation. The ability for other structurally similar small molecule metabolites to elicit insolubilization is key to understanding proteostatic improvements under alternative metabolic states. Similarities in induced insolubilization between βHB and lactate, a key metabolite upregulated during exercise and a critical fuel for neurons, may help partially explain benefits of exercise, especially in aging and NDDs.

<>Each metabolite may have partially overlapping but varied affinity for different proteins, providing a mechanism to both stack and finely target the proteostatic effects in individualized translation applications."[83.L]

[L2] The autophagy-inducing effect of B-Hydroxybutyrate is mediated through SIRT2 and AMPK expression.

"<>Mitochondrial activity and quality control are essential for neuronal homeostasis as neurons rely on glucose oxidative metabolism. The ketone body, D-β-hydroxybutyrate (D-BHB), is metabolized to acetyl-CoA in brain mitochondria and used as an energy fuel alternative to glucose. We have previously reported that D-BHB sustains ATP production and stimulates the autophagic flux under glucose deprivation in neurons; however, the effects of D-BHB on mitochondrial turnover under physiological conditions are still unknown.

<>Sirtuins (SIRTs) are NAD+-activated protein deacetylases involved in the regulation of mitochondrial biogenesis and mitophagy through the activation of transcription factors FOXO1, FOXO3a, TFEB and PGC1α coactivator. Here, we aimed to investigate the effect of D-BHB on mitochondrial turnover in cultured neurons and the mechanisms involved.

<>Results show that D-BHB increased mitochondrial membrane potential and regulated the NAD+/NADH ratio. D-BHB enhanced FOXO1, FOXO3a and PGC1α nuclear levels

in an SIRT2-dependent manner and stimulated autophagy, mitophagy and mitochondrial biogenesis. These effects increased neuronal resistance to energy stress. D-BHB also stimulated the autophagic-lysosomal pathway through AMPK activation and TFEB-mediated lysosomal biogenesis. Upregulation of SIRT2, FOXOs, PGC1α and TFEB was confirmed in the brain of ketogenic diet (KD)-treated mice.
<>Altogether, the results identify SIRT2, for the first time, as a target of D-BHB in neurons, which is involved in the regulation of autophagy/mitophagy and mitochondrial quality control."[83.M]

[M] Phosphatase and Tensin Homolog (PTEN) may promote Alzheimer's progression by promoting excessive autophagy—through enhanced Caspase-3 expression and through AKT inhibition—of healthy brain tissue in the presence of neurofibrillary tangles, which is one reason *not* to experiment with Silymarin if you or someone you love is interested in extending their lifespan while simultaneously suffering from severe neurodegenerative disorders.

[1] "<>Phosphatase and tensin homolog (PTEN) regulates synaptic density in development; however, whether PTEN also regulates synapse loss in a neurodegenerative disorder such as frontotemporal lobar degeneration with Tau deposition (FTLD-Tau) has not been explored.
<>Here, we found that pathological Tau promotes early activation of PTEN, which precedes apoptotic caspase-3 cleavage in the rTg4510 mouse model of FTLD-Tau. We further demonstrate increased synaptic and neuronal exposure of the apoptotic signal phosphatidylserine that tags neuronal structures for microglial uptake, thereby linking PTEN activation to synaptic and neuronal structure elimination. By applying pharmacological inhibition of PTEN's protein phosphatase activity, we observed that microglial uptake can be decreased in Tau transgenic mice.
<>Finally, we reveal a dichotomous relationship between PTEN activation and age in FTLD-Tau patients and healthy controls. Together, our findings suggest that in tauopathy, PTEN has a role in the synaptotoxicity of pathological Tau and promotes microglial removal of affected neuronal structures."[83.N]

[2] "<>The phosphatase and tensin homologue deleted on chromosome 10 (PTEN) negatively regulates intracellular levels of PIP3 and antagonizes the PI3K signaling pathway important for cell survival. The present study determined whether altered distribution of PTEN occurs in Alzheimer's disease (AD) brains.
<>We investigated a possible role for PTEN in postmortem brain tissues from elderly controls and patients with AD using immunoblotting and microscopic analyses. Intense immunolabeling was found in the large neurons such as pyramidal cells. In normal neurons, PTEN was located in the nucleus, the cytoplasm of cell bodies and the proximal portion of apical dendrites. Reduced expression and redistribution of PTEN was seen in the remaining neurons in AD.
<>In addition, PTEN was redistributed in damaged neurons from the nucleus and cytoplasm to neuritic pathology such as intracellular neurofibrillary tangles (NFTs),

neuropil threads and dystrophic neurites within senile plaques in AD hippocampus, subiculum, entorhinal cortex and angular gyrus.
<>Furthermore, double immunofluorescence staining showed dual labeling of intracellular NFTs for PTEN and tau, labeling of some axons for PTEN and phosphorylated neurofilament, and weak labeling of a few reactive astrocytes around senile plaques for PTEN and GFAP. Double labeling of NFTs was observed in a subset of tangle-bearing neurons either for PTEN and GSK3beta or for PTEN and MEK.
<>Thus our results suggest that PTEN delocalized from the nucleus to the cytoplasm and to intracellular NFTs may cause a deregulation of PI3K pathway in the cytoplasm and may induce the nuclear dysfunction of PTEN in AD degenerating neurons."[83.O]

[See: The Tetrad of Human Experience: Psychological Stress Addendum 2: Neurodegeneration]

[See: Anti-Inflammation Cycle Supplementation: Quercetin, EGCg]

[See: Lipolytic Supplementation: Agmatine]

[See: Common Recreational Chemicals: Alcohol: [M]]

[See: Probiotics: Extracellular Vesicles]

[See: Lactic Acid Training]

[See: Myokines]

The Tetrad of Human Experience

Romantic Love

The Experience of Romantic Love is to be considered one of the greatest nootropics alongside exercise, with Serotonin, Dopamine, the Opiate system, and bDNF / NGF working in concert during the early experience of romantic love to promote a form of mood and memory that no other chemical concoction can replicate.
It is plausible to hypothesize that individuals in monogamous & longstanding relationships who engage in infidelity or individuals who are not content to "settle down" with one woman or man are using newly formed romantic relationships as a primordial method to increase their cognition at the potential cost of later life loneliness, and the development of deranged libidos (insufficient sublimation abilities).

"<>Our current knowledge of the neurobiology of romantic love remains scanty. In view of the complexity of a sentiment like love, it would not be surprising that a diversity of biochemical mechanisms could be involved in the mood changes of the initial stage of a

romance. In the present study, we have examined whether the early romantic phase of a loving relationship could be associated with alterations in circulating levels of neurotrophins (NTs).
<>Plasma levels of NGF, BDNF, NT-3 and NT-4 were measured in a total of 58 subjects who had recently fallen in love and compared with those of two control groups, consisting of subjects who were either single or were already engaged in a long-lasting relationship. NGF level was significantly higher ($p < 0.001$) in the subjects in love [mean (SEM): 227 (14) pg/ml] than in either the subjects with a long-lasting relationship [123 (10) pg/ml] or the subjects with no relationship [149 (12) pg/ml]. Notably, there was also a significant positive correlation between levels of NGF and the intensity of romantic love as assessed with the passionate love scale ($r = 0.34$; $p = 0.007$). No differences in the concentrations of other NTs were detected.
<>In 39 subjects in love who-after 12-24 months-maintained the same relationship but were no longer in the same mental state to which they had referred during the initial evaluation, plasma NGF levels decreased and became indistinguishable from those of the control groups. Taken together, these findings suggest that some behavioral and/or psychological features associated with falling in love could be related to raised NGF levels in the bloodstream."[84]

Classical Intelligence

Firstly, it can be said that to develop a high classical intelligence, *Brain Connectivity* must be enhanced, and this depends on high levels of synaptic proliferation (synaptogenesis / + neurite extension), leading to enhanced connectivity between important brain regions associated with intelligence such as the Corpus Callosum[1], a part of the brain that is essential for bridging the gap of communication between the left and right hemispheres of the brain.

Secondly, Environmental Enrichment is an important component of human intelligence, it is a phenomenon that describes the neurogenic potential of engaging in and with novel (non-harmful) stimuli, including social experience, sensory stimuli, toys, & cognitive challenges[2]. The environmental enrichment a human child experiences is often linked to a family's wealth status, because toys, proper education (cognitive challenges), travel (sensory stimuli), social events, less chance of parental divorce, and lower average levels of psychological stress all relate to parental wealth, although parental wealth is only beneficial to a child's neurological development when combined with a household that fosters emotional stability and learning. Because Environmental Enrichment often requires expenditures, money is to be considered an *indirect nootropic* which if spent wisely is capable of stimulating neuronal growth. Of course, money is not always required to stimulate the brain, as exercise will always be the greatest way to improve cognition, and libraries exist for a reason, which ironically are the closest thing left to ancient colleges today (Vis-à-vis: The Academy of Plato, the Lyceum of Aristotle), where divergent thought and intellectual debate is often encouraged, if but passively and unintentionally through the catalogue, rather than dismissed or protested against by supercilious individuals suffering from groupthink. No doubt book burning, both physical

and digital, will eventually return at some point, and oddly it won't be the perverse novellas of sick minds that get burned, but works of science, philosophy, politics, and biographies, making it essential to keep paper copies of any *intellectual* source material you consider inflammatory, or disagreeable towards mainstream thought.

There is no doubt that Environmental Enrichment can only increase a person's intelligence to a certain level, as genetics, and especially the diets and supplementation their mothers chose during their gestation had a massive impact on their neurodevelopment. A baby that in utero was not provided the necessary nutrients will surely be born with a measurable neurodevelopmental disadvantage, yet this can be countered through the careful supplementation of safe neurotrophic antioxidant and nutrient chemicals during the postnatal periods of life, See: Micro-Essays: The Biomedical Baby: Pg. 948.

Note: bDNF may be vital for memory consolidation, but without an adequate number of synapses and neurites, memories will not be capable of being retrieved, and even if they are they will be errored in design owing to a lack of complexity (context).

[1] "<>Objectives: The aim of this study was to assess the size of the corpus callosum in members of Mensa International, which is the world's largest and oldest high-intelligence quotient (IQ) society.
<>Methods: We performed T2-weighted magnetic resonance imaging (Repetition Time, TR = 3200 ms, Time of Echo, TE = 409 ms) to examine the brain of members of Mensa International (Polish national group) in order to assess the size of the corpus callosum. Results from 113 male MENSA members and 96 controls in the age range of 21-40 years were analyzed.
<>Results: The comparative analysis showed that the mean length of the corpus callosum and the thickness of the isthmus were significantly greater in the Mensa members compared to the control groups. A statistically significant difference was also identified in the largest linear dimension of the brain from the frontal lobe to the occipital lobe. The mean corpus callosum cross-sectional area and its ratio to the brain area were significantly greater in the Mensa members.
<>Conclusions: The results show that the dimensions (linear measures and midsagittal cross-sectional surface area) of the corpus callosum were significantly greater in the group of Mensa members than in the controls."[84.1]

[2] "<>Environmental manipulations can enhance neuroplasticity in the brain, with enrichment-induced cognitive improvements being linked to increased expression of growth factors, such as neurotrophins, and enhanced hippocampal neurogenesis. There is, however, a great deal of variation in environmental enrichment protocols used in the literature, making it difficult to assess the role of particular aspects of enrichment upon memory and the underlying associated mechanisms.
<>This study sought to evaluate the efficacy of environmental enrichment, in the absence of exercise, as a cognitive enhancer and assess the role of Nerve Growth Factor (NGF),

neurogenesis and synaptogenesis in this process. We report that rats housed in an enriched environment for 3 and 6 weeks (wk) displayed improved recognition memory, while rats enriched for 6 wk also displayed improved spatial and working memory. Neurochemical analyses revealed significant increases in NGF concentration and subgranular progenitor cell survival (as measured by BrdU+ nuclei) in the dentate gyrus of rats enriched for 6 wk, suggesting that these cellular changes may mediate the enrichment-induced memory improvements.
<>Further analysis revealed a significant positive correlation between recognition task performance and BrdU+ nuclei. In addition, rats enriched for 6 wk showed a significant increase in expression of synaptophysin and synapsin I in the dentate gyrus, indicating that environmental enrichment can increase synaptogenesis. These data indicate a time-dependent cognitive-enhancing effect of environmental enrichment that is independent of physical activity. These data also support a role for increased concentration of NGF in dentate gyrus, synaptogenesis, and neurogenesis in mediating this effect."[84.2]

Emotional Intelligence

Emotional Intelligence is a far more complex phenomenon that Classical or Analytic Intelligence that generally involves a special population of brain cells called Mirror Neurons. Mirror neurons activate when we perform an action, and more importantly, when we observe someone else performing an action, sometimes leading us to experience empathy, but not always sympathy, as that is an even more complex phenomenon that involves conditioning (upbringing, social norms, neurochemistry, religious beliefs, etc.).
It has been shown that certain individuals who could be classified as psychopaths (individuals with pathologically limited empathy) possess decreased mirror neuron activity[1], and this can only be explained by early life psychological conditioning[2]. Something as simple as a crying infant being frequently ignored by parents such as suggested by the antiquated and foolish Ferber Method could cause an infant to develop a dysregulated mirror neuron system and psychopathic traits as a result after reaching later stages of maturity, or what appears to be the more common trend, children raised by selfish parents. Although other forms of childhood abuse cause mental deterioration in later life, emotional neglect is plausible to be the prime causer of psychopathic or narcissistic traits in humans.

[See: Micro-Essays: Altruism, Anthropomorphization, & Morality: Pg. 1025].

[1] "<>Mirror neurons have been associated with empathy. People with psychopathic traits present low levels of empathy. To analyze this, a systematic review of fMRI studies of people with psychopathic traits during an emotional facial expression processing task was performed. The regions of interest were structures associated with the mirror neuron system: ventromedial prefrontal cortex (vmPFC), inferior parietal lobe (IPL), inferior frontal gyrus and superior temporal sulcus. The analysis was also extended to structures related to affective empathy (insula, amygdala and anterior cingulate cortex) and to two more emotional processing areas (orbitofrontal cortex and fusiform gyrus).

<>Hypoactivation was more frequently observed in regions of the mirror neuron system from people with high psychopathic traits, as well as in the emotional processing structures, and those associated with affective empathy, except for the insula, where it presented higher activity. Differences were observed for all types of emotions. The results suggest that the mirror neuron system is altered in psychopathy and their relationship with affective empathy deficits is discussed."[84.3]

[2] "<>The key finding of this study is that disrupted parental bonding is associated with an increased level of adult psychopathic personality. Low maternal care was the key aspect of bonding most associated with psychopathy, while low paternal overprotection (i.e. increased autonomy and lack of regulatory control) was also important, especially in relation to the emotional detachment factor. Childhood physical abuse was also associated with psychopathy, but evidence from regression analyses suggests that bonding is more primary than abuse. Paternal bonding was of significance as it was associated with psychopathy after controlling for maternal care. <>These relationships remained significant after controlling for sex, social adversity and ethnicity. Prospective data on a small group suffering from significant bonding disruption in the first 3 years of life both confirmed links to later psychopathy and provided some validation of the self-report PBI. Findings indicate that maternal bonding and other psychosocial influences should not be ignored in the etiology of psychopathy, and for the first time implicate a role of bonding with the father.
<>Consistent with our hypothesis, low maternal care was the parental variable most strongly associated with both factors of adult psychopathy, reflecting the relatively greater impact of mothers. This finding is consistent with prior research showing that lack of maternal care was more consistently associated with adult psychopathology (including antisocial personality disorder) than paternal care (Enns et al. 2002). <>Nevertheless, our study for the first time demonstrates a significant role of paternal bonding with respect to psychopathy. Low paternal overprotection was associated with higher scores on the emotional detachment factor of psychopathy, even after the effects of maternal care were accounted for. Low paternal overprotection scores reflect a lack of paternal involvement and regulatory control, and poor paternal monitoring and supervision. The significance of paternal bonding is consistent with prior work showing a trend for low paternal overprotection to be associated with increased risk for externalizing disorders (substance-use disorders and antisocial personality disorder) (Enns et al. 2002). Similarly, low paternal involvement has been associated with the affective component of psychopathy (Farrington, 2006). In addition, Wootton et al. (1997) found that poor monitoring and supervision (within the context of a negative parenting composite) was related to greater callous-unemotional traits in 6-to 13-year-old youth.
<>Lack of involvement and monitoring may impair the child's capacity for bonding, and conversely the presence of a protective (albeit strict) father may enhance the emotional connection between father and child, conferring some protection from the development of affective features of psychopathy. Future studies on parental bonding taking both maternal and paternal bonding into account are warranted."[84.4]

Psychological Stress

We know that psychological stress is a socio-sexual phenomenon that is capable of destroying a human life, although I could discuss the most dangerous, most unspoken of, and most insidious psychological stress, childhood sexual abuse, I will refrain from doing so as that will require another book, I am however going to discuss the most prevalent and repeated forms of psychological stress experienced today by humans.

Psychological stress is the primary primordial phenomenon for refining or for destroying a human life. It is both the chronic socio-sexual chaos we encounter in our everyday lives, and the concentrated metaphysical chaos we encounter intermittently. It is an unavoidable stress that damages our minds and our bodies through internal chemical reactions and microbiome toxicity. Similarly to pain, Psychological Stress may benefit a human being, but not through the promotion of memory acquisition, it is instead through the accumulation of wisdom, of fear memories, those of which often become pathological, but serve the purpose of preventing the reoccurrence of the aforementioned stress. Those who have not accrued a sufficient amount of fear memories in their lifetime are in my experience categorizable as undeveloped organisms.

[A] Firstly, there is Social Defeat Stress, this is experienced when an individual or animal is ostracized, embarrassed, or punished (bullied) during an active social confrontation. Social Defeat Stress will not occur if the social confrontation is won through an adequately strong verbal or physical response, which is why it is vital in situations where we know we are correct, we stand up verbally, and if necessary physically, to our aggressors. Passivity is a poison that destroys all, most especially children.

"<>Social defeat can be defined as losing a confrontation between conspecific individuals (Hollis and Kabbaj, 2014). In humans, social defeat has been connected with subjective feelings of being placed in a subordinate or outsider position (Selten and Cantor-Graae, 2005; Selten and Cantor-Graae, 2007; Selten et al., 2013). It has been proposed that social defeat stress plays a central role in the pathogenesis of different psychiatric disorders including psychotic disorders, depression and addiction (Berton et al., 2006; Selten and Cantor-Graae, 2005; Selten and Cantor-Graae, 2007; Selten et al., 2013).
<>A range of studies have been employed to discover the neurobiological impact of social defeat exposures as well as the bio-psycho-social factors moderating the response to social defeat exposure. The subjective nature of the experience of social defeat in humans challenges research on the impact and consequences of social defeat. Studies on humans have therefore mainly focused on different proxy-measures of social defeat exposures, while experimental animal studies have mostly focused on behavioral signs of being in a subordinate or an outsider position after a socially stressful exposure.
<>In the past decades, several animal models of social defeat stress have been developed. Most of these models make use of the natural and predictable behavior of male rodents to defend their territory against intruders, such that a stronger resident–animal defeats an intruder–animal."[84.4A]

[A2] Social Defeat Stress leads to reduced Microtubule stability (a-tubulin changes) leading to a decreased formation of Microtubules, and potentially, the accelerated decay of preexisting Microtubules, resulting in a weakening of Quantum Consciousness. [See: Ion Channels: The Orchestrated Objective Reduction Theory (ORCH-OR) & Ions]
"<>Objective: Microtubule (MT) stability in neurons is vital for brain development; instability is associated with neuropsychiatric disorders. The present study examined the effects of social defeat stress (SDS) on MT-regulating proteins and tubulin polymerization.
<>Methods: After 10 days of SDS, defeated mice were separated into susceptible (Sus) and unsusceptible (Uns) groups based on their performance in a social avoidance test. Using extracted brain tissues, we measured the expression levels of α-tubulin, acetylated α-tubulin, tyrosinated α-tubulin, MT-associated protein-2 (MAP2), stathmin (STMN1), phospho stathmin serine 16 (p-STMN1 [Ser16]), phospho stathmin serine 25 (p-STMN1 [Ser25]), phospho stathmin serine 38 (p-STMN1 [Ser38]), stathmin2 (STMN2), phospho stathmin 2 serine 73 (p-STMN2 [Ser73]), 78-kDa glucose-regulated protein (GRP-78), and CCAAT/enhancer binding protein (C/EBP)-homologous protein (CHOP) using Western blot assay. The tubulin polymerization rate was also measured.
<>Results: We observed increased and decreased expression of acetylated and tyrosinated α-tubulin, respectively, decreased expression of p-STMN1 (Ser16) and increased expression of p-STMN1 (Ser25), p-STMN2 (Ser73) and GRP-78 and CHOP in the prefrontal cortex and/or hippocampus of defeated mice. A reduced tubulin polymerization rate was observed in the Sus group compared to the Uns and Con groups.
<>Conclusion: Our findings suggest that SDS has detrimental effects on MT stability, and a lower tubulin polymerization rate could be a molecular marker for susceptibility to SDS."[84.4B]

[A3] Chronic Social Defeat Stress is partially mitigated behaviorally through Cannabinoid-1 Receptor activity, whereas the lack of CB1r activity substantially exacerbates its cellular toxicity (altered cortisol signaling, inflammation release, & enhanced mortality rate).

"<>Psychosocial stress is one of the main environmental factors contributing to the development of psychiatric disorders. In humans and rodents, chronic stress is associated with elevated inflammatory responses, indicated by increased numbers of circulating myeloid cells and activation of microglia, the brain-resident immune cells. The endocannabinoid system (ECS) regulates neuronal and endocrine stress responses via the cannabinoid receptor 1 (CB1). CB1-deficient mice (Cnr1-/-) are highly sensitive to stress, but if this involves altered inflammatory responses is not known.
<>To test this, we exposed Cnr1+/+ and Cnr1-/- mice to chronic social defeat stress (CSDS). Cnr1-/- mice were extremely sensitive to a standard protocol of CSDS, indicated by an increased mortality rate. Therefore, a mild CSDS protocol was established, which still induced a behavioural phenotype in susceptible Cnr1-/- mice. These mice also showed altered glucocorticoid levels after mild CSDS, suggesting dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Mild CSDS induced weak myelopoiesis in

the periphery, but no recruitment of myeloid cells to the brain. In contrast, mild CSDS altered microglial activation marker expression and morphology in Cnr1-/- mice. These microglial changes correlated with the severity of the behavioural phenotype. Furthermore, microglia of Cnr1-/- mice showed increased expression of Fkbp5, an important regulator of glucocorticoid signalling.
<>Overall, the results confirm that CB1 signalling protects the organism from the physical and emotional harm of social stress and implicate endocannabinoid-mediated modulation of microglia in the development of stress-related pathologies."[84.4C]

[A4] Testosterone increases what I refer to as *Confrontation Confidence*, leading to a decreased potential for Social Defeat Stress to occur. This means that men with higher testosterone levels have a behavioral advantage when confronted with aggressors through decreased natural passivity responses. For women, and most hormonally impoverished men, socio-sexual confidence must be practiced and developed, but for many bodybuilders, powerlifters, & fitness personalities, (confrontation) confidence is purchased by the vial.

"<>Neuro-evolutionary theories describe social anxiety as habitual subordinate tendencies acquired through a recursive cycle of social defeat and submissive reactions. If so, the steroid hormone testosterone might be of therapeutic value, as testosterone is a main force behind implicit dominance drive in many species including humans.
<>We combined these two theories to investigate whether the tendency to submit to the dominance of others is an implicit mechanism in social anxiety (Study-1), and whether this can be relieved through testosterone administration (Study-2). Using interactive eye-tracking we demonstrate that socially anxious humans more rapidly avert gaze from subliminal angry eye contact (Study-1). We replicate this effect of implicit subordination in social anxiety in an independent sample, which is subsequently completely abolished after a single placebo-controlled sublingual testosterone administration (Study-2).
<>These findings provide crucial evidence for hormonal and behavioral treatment strategies that specifically target mechanisms of dominance and subordination in social anxiety."[84.4D]

[B] Secondly, there is what I refer to as *Intellectual Stress*, AKA Burnout Syndrome, or Information Fatigue, it describes the emotionless but strongly experienced psychological stress that we all experience when intellectually overworked, especially in conditions of sleep deprivation, and inadequate diet. This form of stress is initiated by neurotransmitter depletion, or neuroreceptor density decreases. The symptoms of Intellectual Stress predominately revolve around combinations of fatigue, tiredness, intermittently expressed anger (often the result of reduced dopamine availability), apathy, and cynicism.
The psychological "Burnout" experienced by medical workers, or any worker of an intellectually demanding job is explainable by the depletion of their neurotransmitter levels; Dopamine, Serotonin, Glutamine, Acetylcholine, GABA, & Norepinephrine.

"<>Objective The aim of the present study was to investigate the relationship between job burnout and neurotransmitter levels in medical staff.
<>Methods A total of 80 medical staff were enrolled in the study and assessed for occupational burnout using the Maslach Burnout Inventory - General Survey (MBI-GS). The levels of neurotransmitters in the cerebral cortex were analysed using an SP03 encephalofluctuograph.
<>Results The levels of the neurotransmitters γ-aminobutyric acid, 5-hydroxytryptamine (5-HT), norepinephrine (NE), glutamate, acetylcholine (Achl) and dopamine (DA) were significantly lower in men than in women. Medical staff with lower levels of exhaustion had significantly higher neurotransmitter levels than staff with moderate levels of exhaustion. However, there was no significant interaction between sex and exhaustion on neurotransmitter levels. Canonical correlation showed that exhaustion was positively associated with 5-HT and DA, but negatively associated with NE and Achl, regardless of age and sex.
<>Conclusion Neurotransmitter levels in the cerebral cortex were associated with job-related burnout in medical staff. The findings suggest that long-term job-related burnout may lead to behavioural and psychiatric disorders."[84.4E]

[C] Thirdly, there is Emotional Stress which is a far more complicated type of stress that is defined by the generation of intense feelings and emotions, coupled with physiological cellular responses, such as heightened cortisol release. Emotional Stress is often facilitated through reminiscing—through recollecting thoughts involving family members, romantic partners, friends, or even after experiencing Social Defeat Stress. For simplicity, we will refer to Emotional Stress as the act of "Grieving".

[1] Complicated Grief (Prolonged Grief) results in activation of the Nucleus Accumbens, which is part of the dopaminergic Reward Center in the brain, meaning that those who continue to grief long after emotional trauma are, in my view, maintaining a strong connection, at the cost of behavioral dysregulation and emotional instability, to their *grief memories* through dopaminergic activity, and this would be only possible through consistent and ritualistic voluntary reminiscing. I do not find the attachment, or some may say "addiction" to grief some display to be immoral or always unhealthy, as for many the fear of forgetting a lost loved one is almost as painful as the fear of the original loss in question, there is therefore no reason, especially when dealing with scenarios involving the loss of a child, that someone should not be allowed many, many years to grieve—to maintain the strength of their memories.

"<>Complicated grief (CG) occurs when an individual experiences prolonged, unabated grief. The neural mechanisms distinguishing CG from noncomplicated grief (NCG) are unclear, but hypothesized mechanisms include both pain-related activity (related to the social pain of loss) and reward-related activity (related to attachment behavior). Bereaved women (11 CG, 12 NCG) participated in an event-related functional magnetic resonance imaging scan, during grief elicitation with idiographic stimuli.

<>Analyses revealed that whereas both CG and NCG participants showed pain-related neural activity in response to reminders of the deceased, only those with CG showed reward-related activity in the nucleus accumbens (NA). This NA cluster was positively correlated with self-reported yearning, but not with time since death, participant age, or positive/negative affect.
<>This study supports the hypothesis that attachment activates reward pathways. For those with CG, reminders of the deceased still activate neural reward activity, which may interfere with adapting to the loss in the present."[84.4F]

[2] Complicated Grief results in epigenetic immunodepression, leading me to believe that emotional stress and the loss of an interpersonal attachment is capable of rapidly stimulating a natural systemic cellular trend towards weakened immunodefense leading to the increased probability of death, and for some, the sooner afterlife reunion of a lost loved one, especially in the cases of elderly individuals.

"<>The "widowhood effect" (i.e., morbidity/mortality in recently bereaved spouses) may be related to changes in immune function, but little is known about the impact of bereavement on gene transcription in immune cells. This study examined how Complicated Grief and Non-complicated Grief responses to bereavement differentially affect leukocyte gene expression. Genome-wide transcriptional profiling and bioinformatic analyses were completed on 63 older adults. Thirty-six of them had lost their spouse/partner on average 2 years ago, and 27 were nonbereaved, married controls. Twelve of the bereaved participants met criteria for Complicated Grief. <>Compared to nonbereaved controls, bereavement (both Complicated Grief and Non-complicated Grief) was associated with upregulated expression of genes involved in general immunologic activation and a selective downregulation of genes involved in B lymphocyte responses. <>However, Complicated Grief and Non-complicated Grief differed markedly in their expression of Type I interferon-related transcripts, with Non-complicated Grief subjects showing substantial upregulation relative to nonbereaved controls and Complicated Grief subjects showing substantial downregulation. Bereavement significantly modulates immune function gene expression. The magnitude of bereavement-related distress (i.e., Complicated Grief vs. Non-complicated Grief) is linked to differential patterns of transcription factor activation and gene expression involved in innate antiviral responses. <>These findings provide a molecular framework for understanding the health effects of bereavement, as well as new insights into the particular gene modules that are most sensitive to the individual's psychological response to loss."[84.4G]

[D] Finally, there is Chronic Unpredictable Stress (CUS), the form of stress that involves a combination or singular intermittent and unmentioned forms of stress such as the experience of pain (foot shocks in mice), drowning (forced swim tests), noise pollution, and sleep deprivation or disruption, which in human scenarios only serve to compound and exacerbate the previous major forms of stress. This form of stress, due to often negatively impacting sleep, and causing the greatest increases in cortisol levels, results in the greatest perturbations in neurotrophic chemicals, primarily bDNF.

[1] CUS results in decrease bDNF expression through hypermethylation (inactivation) in adolescent brains

"<>Early life stress alters brain-derived neurotrophic factor (BDNF) promoter IV methylation and BDNF expression, which is closely related to the pathophysiological process of depression. However, the role of abnormal methylation of BDNF induced by stress during adolescence due to depression has not yet been clarified.
<>In this study, adolescent mice were exposed to chronic unpredictable mild stress (CUMS). Depression-like behaviors, BDNF promoter IV methylation, expression of DNA methyltransferases (DNMTs), demethylation machinery enzymes, BDNF protein levels, and neuronal development in the prefrontal cortex (PFC) and hippocampus (HIP) were assessed in adolescent and adult mice. The DNMT inhibitor, 5-Aza-2-deoxycytidine (5-AzaD), was used as an intervention.
<>Stress in adolescence induces behavioral dysfunction, elevated methylation levels of BDNF promoter IV, changes in the expression of DNMT, and demethylation machinery enzymes in adolescent and adult mice. Additionally, the stress in adolescence induced lower levels of BDNF and abnormal hippocampal doublecortin (DCX) expression in adolescent and adult mice. However, DNMT inhibitor treatment in adolescent-stressed mice relieved the abnormal behaviors, normalized the methylation level of BDNF promoter IV, BDNF protein expression, expression of DNMTs, and demethylation machinery enzymes, and improved the neuronal development of adult mice.
<>These results suggest that stress in adolescence induces short- and long-term hypermethylation of BDNF promoter IV, which is regulated by DNMTs, and leads to the development of depression."[84.4H]

[2] Chronic Mild Stress (a *milder* form of CUS) increases Caspase-3 in the brain, leading to enhanced cellular apoptosis, and although CUS increases NGF, this is compensatory due to increased Matrix Metalloproteinases in the brain which reduce the active form of NGF. Therefore, we know that Chronic Stress increases inflammation in the brain, and that it perturbs active NGF signaling.

"<>Stress is generally a beneficial experience that motivates an organism to action to overcome the stressful challenge. In particular situations, when stress becomes chronic might be harmful and devastating. The hypothalamus is a critical coordinator of stress and the metabolic response; therefore, disruptions in this structure may be a significant cause of the hormonal and metabolic disturbances observed in depression. Chronic stress induces adverse changes in the morphology of neural cells that are often associated with a deficiency of neurotrophic factors (NTFs); additionally, many studies indicate that insufficient NTF synthesis may participate in the pathogenesis of depression.
<>The aim of the present study was to determine the expression of the nerve growth factor (NGF) in the hypothalamus of male rats subjected to chronic mild stress (CMS) or to prenatal stress (PS) and to PS in combination with an acute stress event (AS). It has been found that chronic mild stress, but not prenatal stress, acute stress or a combination of PS with AS, decreased the concentration of the mature form of NGF (m-NGF) in the

rat hypothalamus. A discrepancy between an increase in the Ngf mRNA and a decrease in the m-NGF levels suggested that chronic mild stress inhibited NGF maturation or enhanced the degradation of this factor. We have shown that NGF degradation in the hypothalamus of rats subjected to chronic mild stress is matrix metalloproteinase-dependent and related to an increase in the active forms of some metalloproteinases (MMP), including MMP2, MMP3, MMP9 and MMP13, while the NGF maturation process does not seem to be changed.
<>We suggested that activated MMP2 and MMP9 potently cleave the mature but not the pro- form of NGF into biologically inactive products, which is the reason for m-NGF decomposition. In turn, the enhanced expression of Ngf in the hypothalamus of these rats is an attempt to overcome the reduced levels of m-NGF.
<>Additionally, the decreased level of m-NGF together with the increased level of pro-NGF can decrease TrkA-mediated neuronal survival signaling and enhance the action of pro-NGF on the p75(NTR) receptor, respectively, to evoke pro-apoptotic signaling. This hypothesis is supported by elevated levels of the caspase-3 mRNA in the hypothalamus of rats subjected to chronic mild stress."[84.4I]

Psychological Stress Addendum 1: The Microbiome

[A] Apparently, Lactobacilli counts in the small intestine decrease after exposure to chronic stress due to reduced Vagus Nerve activity by way of Brunner's glands secretions, thus illustrating strange interconnectedness of the gut-brain axis.

"<>Negative psychological states impact immunity by altering the gut microbiome. However, the relationship between brain states and microbiome composition remains unclear. We show that Brunner's glands in the duodenum couple stress-sensitive brain circuits to bacterial homeostasis. Brunner's glands mediated the enrichment of gut Lactobacillus species in response to vagus nerve stimulation. Cell-specific ablation of the glands markedly suppressed Lactobacilli counts and heightened vulnerability to infection.
<>In the forebrain, we mapped a vagally mediated, polysynaptic circuit connecting the central nucleus of the amygdala to Brunner's glands. Chronic stress suppressed central amygdala activity and phenocopied the effects of gland lesions. Conversely, excitation of either the central amygdala or parasympathetic vagal neurons activated Brunner's glands and reversed the effects of stress on the gut microbiome and immunity.
<>The findings revealed a tractable brain-body mechanism linking psychological states to host defense."[84.4J]

[B] Pregnant mice subjected to restraint-stress produce offspring that have decreased Lactobacilli populations, and increased stress sensitivity.

"<>Early-life adverse experiences, including prenatal stress (PNS), are associated with a higher prevalence of neurodevelopmental, cardiovascular and metabolic disorders in affected offspring. Here, in a rat model of chronic PNS, we investigate the impact of late gestational stress on physiological outcomes in adulthood. Sprague-Dawley pregnant

dams were subjected to repeated restraint stress from embryonic day 14 to day 20, and their male offspring were assessed at 4 months of age.
<>PNS induced an exaggeration of the hypothalamic-pituitary-adrenal (HPA) axis response to stress, as well as an elevation of blood pressure and impairment of cognitive function. Altered respiratory control was also observed, as demonstrated by increased variability in basal respiratory frequency and abnormal frequency responses to both hypoxic and hypercapnic challenges. PNS also affected gastrointestinal neurodevelopment and function, as measured by a decrease in the innervation density of distal colon and an increase in the colonic secretory response to catecholaminergic stimulation.
<>Finally, PNS induced long lasting alterations in the intestinal microbiota composition. 16S rRNA gene 454 pyrosequencing revealed a strong trend towards decreased numbers of bacteria in the Lactobacillus genus, accompanied by elevated abundance of the Oscillibacter, Anaerotruncus and Peptococcus genera in PNS animals. Strikingly, relative abundance of distinct bacteria genera significantly correlated with certain respiratory parameters and the responsiveness of the HPA axis to stress.
<>Together, these findings provide novel evidence that PNS induces long-term maladaptive alterations in the gastrointestinal and respiratory systems, accompanied by hyper-responsiveness to stress and alterations in the gut microbiota."[84.4K]

[C] Maternal separation between child and mother (rhesus monkeys) causes a "significant" but temporary decrease in predicted Lactobacillus counts in the child following separation.

"<>The integrity of the indigenous microflora of the intestines after maternal separation was investigated in infant rhesus monkeys to determine whether psychological stress may lead to an internal environment conducive to pathogen infection. The stability of the indigenous microflora were estimated by enumeration of total and gram-negative aerobic and facultatively anaerobic bacterial species, specifically Lactobacilli, from coprocultures taken before and after maternal separation. In addition, behavioral and cortisol responses to separation were correlated to the microflora.
<>A significant decrease in fecal bacteria, especially Lactobacilli, was evident on day 3 postseparation, with a return to baseline by the end of the week. The drop in the microflora was correlated with the display of stress-indicative behaviors, but not with cortisol secretion.
<>In addition, infants who displayed numerous stress-indicative behaviors were more susceptible to opportunistic bacterial infection. These results suggest that strong emotional reactions to disruption of the mother-infant bond may increase vulnerability to disease."[84.4L]

Psychological Stress Addendum 2: Neurodegeneration

[A] The reduced ability to cope with stress results in accelerated Tau deposition, leading to worsening cognitive decline, and the progression towards dementia.

"<>Objective: Research in animals has shown that chronic stress exacerbates tau pathology. In humans, psychological stress has been associated with higher risk of Alzheimer disease clinical syndrome. The objective of this cross-sectional study was to assess the hypothesis that stress coping ability (assessed via the Brief Resilience Scale [BRS]) is associated with tau burden and to evaluate whether these associations differed by sex and amyloid status (A+/A-) in cognitively unimpaired (CU) older adults.
<>Methods: We included 225 CU participants (mean age 70.4 ± 10.2 years, 48% female) enrolled in the population-based Mayo Clinic Study of Aging who completed the BRS and underwent amyloid-PET (Pittsburgh compound B-PET) and tau-PET (AV1451-PET). We fitted multiple regression and analysis of covariance models to assess the associations between BRS and tau-PET and the interaction with amyloid status and sex. We focused on entorhinal cortex (ERC) tau burden and also performed voxel-wise analyses. Age, sex, education, depression, and anxiety were considered as covariates.
<>Results: Higher stress coping ability was associated with lower tau burden in the medial temporal lobe (including ERC) and occipito-temporal and cuneal/precuneal cortices. The association was present in both A+ and A- but weaker in A- CU older adults. There was an interaction between amyloid status and stress coping ability that was restricted to the medial temporal lobe tau such that A+ CU older adults with lower stress coping abilities showed higher tau. There were no significant interactions between stress coping and sex.
<>Conclusions: A faster termination of the stress response (higher coping ability) may limit the negative effects of stress on tau deposition. Conversely, lower stress coping ability may be an early sign of accumulating tau pathology. Longitudinal studies are warranted to clarify whether stress mechanisms act to exacerbate tau pathology or tau influences stress-related brain mechanisms and lowers the ability to cope with stress."[84.4M]

[B] Another study showing that chronic stress exacerbates Amyloid-beta and Tau accumulation in the brain. Although most understand that diet and inactivity are the prime inducers and facilitators of dementia, the exposure to psychological stress is sure to play a major role in the development and exacerbation of neurodegenerative conditions.

"<>The etiology of the more common (sporadic) forms of Alzheimer's disease (AD) remains unknown, although age is the most important risk factor. Nevertheless, interactions between environmental risk factors and genetic background may also influence the onset and progression of sporadic AD. Chronic stress, associated with altered memory and other neurological processes, is thought to influence the pathogenesis of AD. Hence, we evaluated the effect of unpredictable and consecutive chronic mild stressors on the onset of an AD-related pathology in the Tg2576 mouse line that overexpresses the human amyloid-β protein precursor with the Swedish mutation (hAβPP(Swe)).
<>Two months after exposure to chronic mild stress, 4 month-old animals that normally display no pathological features of AD, not only expressed pathological markers but also

experienced cognitive dysfunction in the Morris water maze test. These findings suggest that chronic mild stress accelerates the onset of cognitive impairment and produces an increase in hippocampal amyloid-β and phospho-tau levels on a background of AD susceptibility."[84.4N]

[C] Exposing male mice to Subordination Stress, a form of Social Defeat Stress, accelerates neuronal and systemic cellular senescence through enhanced p16 expression, and excessive autophagy (cellular death). This offers greater insight into masculine biochemistry, and brings me back to the Freudian point that social passivity is poison, especially in males, and the continual push in postmodern egalitarian societies to demasculinize and quell the confidence in young boys will not only castrate them psychologically, but *cellularly*.

"<>Life stress can shorten lifespan and increase risk for aging-related diseases, but the biology underlying this phenomenon remains unclear. Here we assessed the effect of chronic stress on cellular senescence-a hallmark of aging. Exposure to restraint stress, a psychological non-social stress model, increased p21Cip1 exclusively in the brains of male, but not female mice, and in a p16Ink4a-independent manner. <>Conversely, exposure to chronic subordination stress (only males were tested) increased key senescent cell markers in peripheral blood mononuclear cells, adipose tissue and brain, in a p16Ink4a-dependent manner. p16Ink4a-positive cells in the brain of chronic subordination stress-exposed mice were primarily hippocampal and cortical neurons with evidence of DNA damage that could be reduced by p16Ink4a cell clearance. Clearance of p16Ink4a-positive cells was not sufficient to ameliorate the adverse effects of social stress on measured metrics of healthspan. Overall, our findings indicate that social stress induces an organ-specific and p16Ink4a-dependent accumulation of senescent cells, illuminating a fundamental way by which the social environment can contribute to aging."[84.4O]

Psychological Stress Addendum 3: Hormones

[A] Chronic stress exposure damages the testes through ROS formation leading to reduced Testosterone production.

"<>Several studies have suggested that stress and ageing exert inhibitory effects on rat Leydig cells. In a pattern similar to the normal process of Leydig cell ageing, stress-mediated increases in glucocorticoid levels inhibit steroidogenic enzyme expression that then results in decreased testosterone secretion. We hypothesized that chronic stress accelerates the degenerative changes associated with ageing in Leydig cells.
<>To test this hypothesis, we established a model of chronic stress to evaluate stress-induced morphological and functional alterations in Brown Norway rat Leydig cells; additionally, intracellular lipofuscin levels, reactive oxygen species (ROS) levels and DNA damage were assessed.

<>The results showed that chronic stress accelerated ageing-related changes: ultrastructural alterations associated with ageing, cellular lipofuscin accumulation, increased ROS levels and more extensive DNA damage were observed. Additionally, testosterone levels were decreased. This study sheds new light on the idea that chronic stress contributes to the degenerative changes associated with ageing in rat Leydig cells in vivo."[84.4P]

[B] Psychological stress in males enhances Glucocorticoid receptors (Cortisol activity) which dampens NMDA receptor function (glutamine receptor degradation), resulting in the development of cognitive impairment and depression, whereas Estrogen counteracts the effect of psychological stress in the brains of female mice through promoting NMDA receptor function (glutamine receptor synthesis).

"<>Animal and human studies have found that males and females show distinct stress responses. Recent studies suggest the contribution of estrogen in the brain to this sexual dimorphism. Repeated stress has been found to impair cognitive behaviors via suppressing glutamatergic transmission and glutamate receptor surface expression in pyramidal neurons of prefrontal cortex (PFC) in male rats.
<>On the contrary, female rats exposed to the same stress paradigms show normal synaptic function and PFC-mediated cognition. The level of aromatase, the enzyme for the biosynthesis of estrogen, is significantly higher in the PFC of females than males. The stress-induced glutamatergic deficits and memory impairment are unmasked by blocking estrogen receptors or aromatase in females, suggesting a protective role of estrogen against the detrimental effects of repeated stress."
"<>In males, repeated stress triggers the activation of glucocorticoid receptors (GR). GR bind to glucocorticoid response element (GRE) on the promoters of downstream genes, triggering the increased glutamate receptor ubiquitination and degradation. In females, estrogen activates estrogen receptors (ER), which bind to estrogen response element (ERE) and enhance the transcription of synaptic plasticity genes that promote the synthesis and exocytosis of glutamate receptors, therefore counteracting the stress-induced depressing effects."[84.4Q]

[C] Human tears reduce Testosterone in men when inhaled through the release of a chemosignal in tears.

"<>Rodent tears contain social chemosignals with diverse effects, including blocking male aggression. Human tears also contain a chemosignal that lowers male testosterone, but its behavioral significance was unclear. Because reduced testosterone is associated with reduced aggression, we tested the hypothesis that human tears act like rodent tears to block male aggression.
<>Using a standard behavioral paradigm, we found that sniffing emotional tears with no odor percept reduced human male aggression by 43.7%. To probe the peripheral brain substrates of this effect, we applied tears to 62 human olfactory receptors in vitro. We identified 4 receptors that responded in a dose-dependent manner to this stimulus.

Finally, to probe the central brain substrates of this effect, we repeated the experiment concurrent with functional brain imaging.
<>We found that sniffing tears increased functional connectivity between the neural substrates of olfaction and aggression, reducing overall levels of neural activity in the latter. Taken together, our results imply that like in rodents, a human tear–bound chemosignal lowers male aggression, a mechanism that likely relies on the structural and functional overlap in the brain substrates of olfaction and aggression. We suggest that tears are a mammalian-wide mechanism that provides a chemical blanket protecting against aggression."[84.4R]

Consciousness

Consciousness is defined perfectly in the following study by Clint J Perry and Lars Chittkaas [A] as creatures capable of *foresight* i.e. the ability to plan for the future through mental processing, such as with anticipation, problem solving, & imagination.
Many different insects have been found to possess "Domain-General Problem Solving Abilities", which are indicators of consciousness, the ability to engage in abstract thinking and foresight. The older theory on insect intelligence came from the Neural-Toolkit hypothesis, which is most logically explained as inherited motor and visual memories necessary for survival, but this hypothesis although intelligent is not directly related to consciousness.
If even spiders possess consciousness, is it moral for us to fear them, or attempt to kill them? There is much to be learned from Asian Religions which speak of the sanctity of all life, even the smallest forms. I will clarify that I do not believe if we step on a bug, we have committed a sin, or non-religious moral grievance against "Nature", but it is interesting to learn that we exist in milieus that are cohabitated with other lifeforms that possess similar, if far less sophisticated neural architecture and mental processes.

I do believe Terrence McKenna was intelligent to posit the Stoned Ape Theory as an explanation for the evolution of consciousness, but it was biased by his predilection and liking for potent mind-altering substances. Enhancing neurite outgrowth and neurogenesis through the consumption of non-psychoactive mycochemicals would obviously promote intelligence and thus promote consciousness in our ancestors, and it does make perfect sense that the consumption of psychedelic mycochemicals such as psilocybin would have contributed to the development of cultural and religious thought patterns, but there are far more provable reasons for the development of human consciousness, such as locomotion, repeated retrovirus infection, and *aromatic compounds*. I do believe Plant and fungi chemicals have played a large role in the evolution and mutation of the brains of our greatest ancestors, especially the exposure to Volatile Organic Compounds.

[A] Introduction

"<>The diverse types of behaviors in insects and other arthropods (e.g. in nest construction, defense and foraging behavior) have often been argued to be a result of relatively fixed (genetically pre-programmed) routines which require no learning, suggesting that such animals have little behavioral flexibility . We review new literature indicating that arthropods are able to make decisions with a basic recognition of their goals and problems they face. We suspect that such recognition is rooted in the fact that meaningful interpretation of the input from sensors such as imageforming eyes is only possible when one takes into account one's own intentions to move (or not move) these sensors. Such notions of links between action and perception date back to the 1800's – for example, Johannes Purkinje's work (1825) on why active, voluntary movement of the eye does not cause perception of movement of the visual scene, but pressing the eye with a finger does. This 'efference copy' phenomenon has been studied neurophysiologically in crustaceans and insects, where its neural underpinnings are now understood in unparalleled detail. Building on such simple forms of predicting the immediate future, we explore cases which seem to us to indicate that behavioral flexibility in arthropods is linked to a prediction of the sensory input as a consequence of their own actions"

(1) Route planning in Spiders

"<>An example of foresight is planning, behavior done in the service of future needs. There are several observations of the jumping spider Portia fimbriata in the wild behaving as though it was planning, including detouring away from their prey, in sometimeslong and circuitousroutes, before heading towards it, appearing to avoid a frontal attack and to surprise the prey. In laboratory experiments, P. fimbriata were placed on top of a cylinder where they could see two elevated perches, one containing prey (a dead Eriophora pustulosa covered in acrylic to avoid olfactory cues). To retrieve the prey, the spider had to descend from the cylinder to the floor, where she could no longer see the prey, and climb an array of poles connected to the prey-containing perch. In a series of different setups, for the spider to reach the prey she had to often walk away from the prey and/or walk past where the incorrect route began. With no prior experience with the setups nor any other sensory information regarding the prey besides seeing it while on the cylinder, spiders chose (contacted the start of a pole array) the correct route significantly more often than the incorrect route, suggesting that these spiders recognized their goal (prey) and the spatial problem they faced (non-straightforward route), envisaged potential actions, and planned their route while atop the cylinder."

(2) Behavioral Flexibility through social learning in Bumblebees

"<>A recent study explored bumblebees' behavioral flexibility by requiring bees to transport a ball to a defined location in order to receive a reward (sucrose solution). Bumblebees (Bombus terrestris) learned how to solve the task through social demonstration, observing that they could move one of three possible balls (the furthest

one from the center) into a central area to obtain reward. When later tested on their own, the observer bees chose not the furthest ball from the center but the closest ball to the center. They did this even when the closest ball was colored black instead of the trained yellow. Importantly, observers had no prior experience with rolling the balls themselves (i.e. no opportunity for operant learning); they also did not simply land near the target area and move the ball that happened to be closest, but instead flew directly to the closest ball after surveying the spatial arrangement. These results indicate that instead of simply copying a learned technique, bumblebees spontaneously improved on the strategy used by the demonstrator, suggesting that they recognized the target of their actions ('ball in goal'), envisioned multiple routes to that target and chose the most efficient one."

(3) Tool use in Ants

"<>The above example already indicates a basic form of tool use in an insect, but even more impressive examples of behavioral flexibility can be seen when animals flexibly select the appropriate toolsin problem solving. Maa´k et al. investigated tool selection and use in two species of ants(Aphaenogastersubterranea and Aphaenogaster senilis) by giving them the choice between different types of objects in a foraging situation that required bringing liquid food (honey water) back to the nest. Earlier observations indicated that several ant species use debris to sponge up such liquid food. This behavior was flexible in terms of the types of objects ants would choose and utilize for food transport. Ants did not only use objects that they commonly encounter, like soil and twigs, but also objects not available in the wild, such as strings and foam. Impressively, over trials ants preferred to utilize paper or sponge, the most efficient (absorbent) materials available. Ants also cut the sponge into smaller pieces for easier transport. These results show that the ants' ability to use various objects as tools is not rigid and can be flexible in terms of type of objects used and optimal choice of tool with regards to the goal at hand."

(4) The Evolution of Foresight

"<>One could imagine that arthropods have pre-programmed behavioral routines for each environmental situation they may come across. But for many species, including those displaying the behavioral flexibility described above, this would likely require an implausibly large number of routines. An extensive array of specialized neural circuits (modules) would presumably be required to solve just the likely challenges. However, this domain specific tool kit would still not allow an animal to solve novel problems, outside those encountered in their species' evolutionary history. Thus, in addition to postulating even more neural circuits to cope with such challenges, adherents of the neural tool-kit hypothesis would have to explain why arthropods would have evolved specialized mechanisms for scenarios they are unlikely to have encountered before a pesky experimenter ever confronted the animals with them. We therefore favor the notion that at least some arthropods have a more domain general problem-solving ability, which allows much more behavioral flexibility.

"<>We've argued so far that foresight (outcome expectation) may explain the above discussed examples of behavioral flexibility in arthropods. It has also been argued that motor control and simple forms of learning (e.g. classical conditioning) are expressed behaviorally as a result of comparing memory with expected outcome. Indeed, prediction error learning rules, likely occurring in all animals, are isomorphic to efference copy systems, both relying on the difference between experienced and predicted events for generating a teaching signal and for perception, respectively. The fact that these cognitive processes are displayed within such small brains, suggests that outcome expectations might be a fundamental element of cognitive behavior."
"<>The circuitry for more advanced planning skills might not be too extensive to accommodate in an arthropod brain either, as shown by neural network architectures that support the outcome predictions of simulated robot actions. Recently, Barron & Klein have postulated that the central complex (an evolutionary ancient arthropod brain structure) might support such consciousness-like phenomena, since it is not just crucial for action selection, but also integrates information from the visual periphery, the animal's own motion, its memories and its internal motivational states. Among the insects, however, the most impressive behavioral and cognitive flexibility is found in a few clades of the Hymenoptera that have highly enlarged mushroom bodies, and it is therefore appropriate to explore whether these structures (and their neural circuitry) support the unusual behavioral capacities of these insects.
<>Indeed, even simple models of the bee mushroom body circuit can support relatively complex forms of learning and memory, but more work is needed to explore how any neural circuit might mediate the elaborate problem-solving skills and prospective cognition observed in these animals. We suspect the spontaneous activities and oscillations reported in various areas of arthropod brains (even in resting states) are at the heart of the mental exploration of possible solutions to complex and unexpected challenges."[84.4.1]

[B] Plants are not "Conscious" due to lacking the ability to engage in Forethought, this does not mean that plants are not Intelligent, but likened to ChatGPT, or Meta, just because they are *programmed* in such a way as to survive, to breed, or to defend themselves in intelligent ways, does not mean they are sentient and conscious.

"<>Proponents claim that plants exhibit proactive behaviors, not just reactive ones, and that this intentional, proactive behavior indicates consciousness (Calvo 2017; Calvo and Friston 2017; Trewavas 2017; Latzel and Münzbergová 2018). Most of their examples involve the growth of roots, shoots, or climbing vines toward a goal or away from harm (e.g., Shemesh et al. 2010). But these examples always involve sensing and following a stimulus trail ("responses to stimuli"; "proactively sampling": Calvo et al. 2017; Calvo and Friston 2017), which is reactive, not proactive. Rather than reflecting consciousness, it seems that plant growth patterns are preprogrammed to follow environmental clues.
<>Truly proactive behavior that indicates consciousness would be to find the goal in the absence of a sensory trail, based on a mental map of the surrounding environment (Klein

and Barron 2016; Feinberg and Mallatt 2018: p. 58) and on memories of this mapped space (Feinberg and Mallatt 2016a: pp. 114-115)."
"<>Plant movements resemble those of the roundworm Caenorhabditis elegans (C. elegans), which is the representative nonconscious animal (Barron and Klein 2016: Klein and Barron 2016). When foraging in soil for its bacterial food, this worm continually uses many senses (taste, smell, touch, moisture) to track and find the richest bacterial patches (Ardiel and Rankin 2010; also see Gang and Hallem 2016), and it usually succeeds, especially when, upon losing the trail, it conducts a thorough and patterned search.
<>The preprogrammed searching of C. elegans, as a characteristic nonconscious behavior, resembles the winding growth movements of plants (circumnutation) that help them to find targets. It is therefore wrong to claim (Calvo 2017) that of these two organisms, only C. elegans lacks "goal-directed behavior" (incorrect because foraging is goal-directed by definition, the goal being to find the food or other resource). It is also erroneous to claim that "anything beyond their immediate surroundings eludes C. elegans," because C. elegans follows the sensory trail out of its immediate surroundings and eventually finds distant food. And to claim that C. elegans "is unable to go beyond the here and now" is also incorrect because this worm persists in following the sensory trail for as long as it takes to achieve the goal.
<>These observations show that certain nonconscious organisms can do impressive things without any proactive behavior. Another splendid example is the efficient foraging by fungal mycelial networks in the forest floor (Fricker et al. 2017), fungi also being nonconscious by our criteria. And recall how impressive but nonconscious foraging can be aided by attractant breakdown (Claim 1 above: Tweedy et al. 2020)."[84.4.2]

[C] The evolution of Consciousness requires increased locomotion, and this could explain the intriguing intelligence of the previous animal species, and provide us with a better understanding of the neurotrophic effects of Lactic Acid, for why else would a waste product associated with enhanced locomotion in human beings exert a neurotrophic effect except to promote survivalism through improved neurological function?

"<>There is currently no consensus regarding the nature and function of consciousness. Proposals cover a wide range of constructs. At one end of this spectrum consciousness may be cast in a privileged relation to human language (Macphail, 1998, Macphail, 2000), while at the other it is construed as a fundamental feature of the world on a par with mass, charge, and space-time (Chalmers, 1995, Chalmers, 1996). The explanandum itself is ill defined, in other words. In such a situation specific conjectures regarding the nature, function or origin of consciousness have a special role to play by providing a focus for attempts to determine the extent to which they fit available facts. In what follows one such specific proposal will be elaborated. Consciousness will be interpreted as a biological function evolved by mobile animals as a solution to neural logistics problems inherent in the control of orientation to their surroundings. The interpretation is motivated by the conspicuous absence from the contents of consciousness of two significant classes of information known to be present in brains, one on the afferent and the other on the efferent side of neural function. In fact, the thoroughness of their

exclusion from consciousness suggests that their absence represents a design feature of consciousness providing important clues to its nature and biological function. This in turn helps constrain conceptions of its neural implementation as well as the search for its origin in the phylogeny of life forms."[84.4.3]

[See: Ion Channels: The Orchestrated Objective Reduction Theory (ORCH-OR) & Ions]

Engrams

An Engram is a pattern of neural activity that forms a memory trace, the encoding of memories in the brain. LTP is necessary for engram formation, and engram maintenance, through enhancing synaptic transmission and synaptic efficiency (Neurotransmitter release, AMPA receptor formation) in neuronal populations.

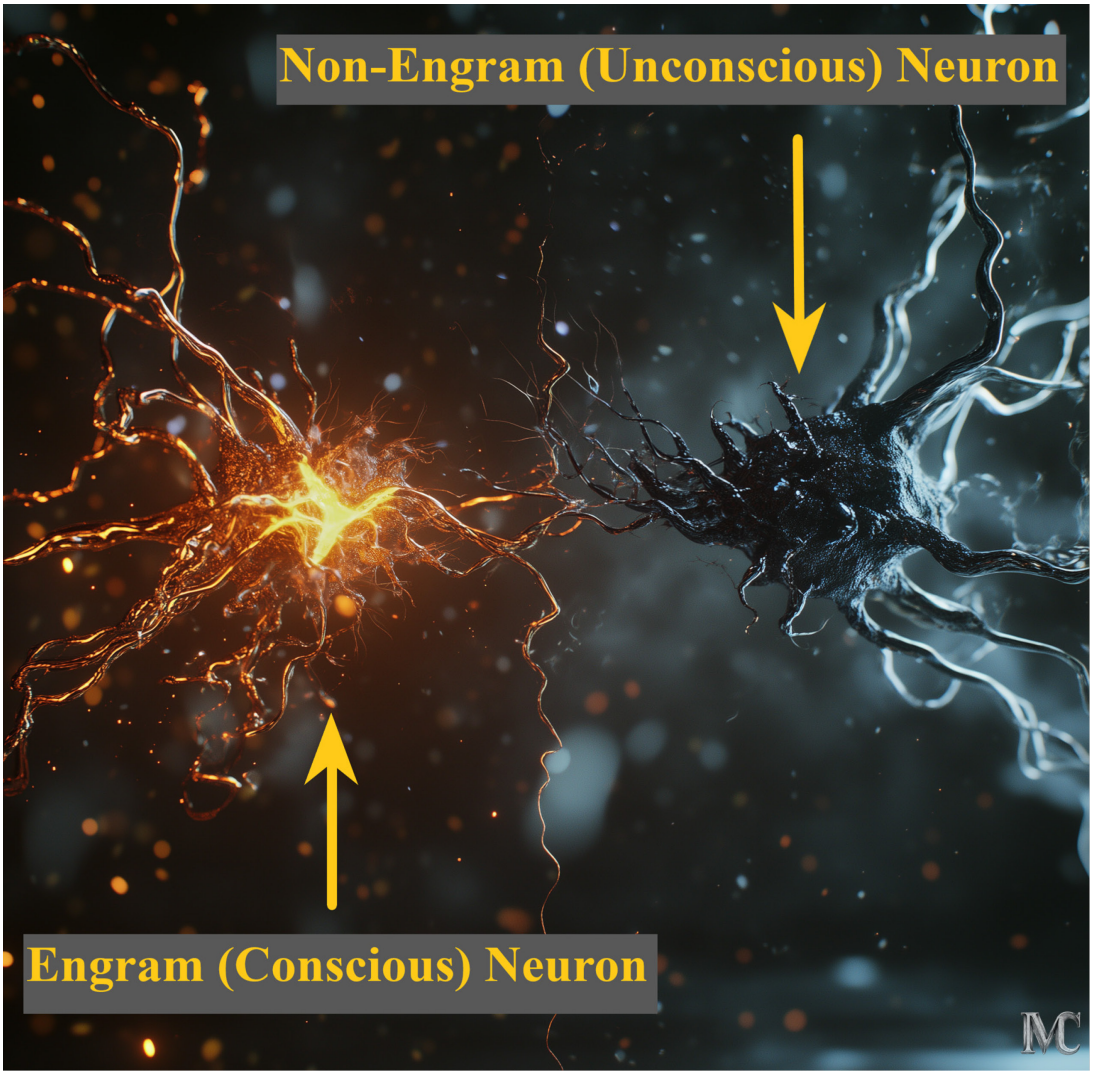
Neurons are classified as either Engram Neurons or Silent-Engram Neurons. Engram Neurons are necessary for encoding and storing information, specifically long-term memory. Silent-Engram Neurons, which make up the majority of neurons in the brain, are necessary for short-term memory, and processes such as perception, motor control, & attention.

Richard Semon's idea of an Engram coincided, and likely postdated Sigmund Freud's elaboration on LTP, synapses, and consciousness, in his *Project for a Scientific Psychology*, written from 1895-1899.

It is my hypothesis, directly inspired by Freud's Project, that at the most basic level, without the consideration of synapses, neurons store information (sensory waves, electromagnetic waves) in the form of ***Hypercomplex Action Potential Signatures*** (similar to the binary states within a hard drive), which differ in amplitude, frequency, and timing, resulting in the formation of "information" that can be stored in each individual neuron. Because memories are often composed of different sensory waves, different subsets of neurons, and a greater number of neurons are required to store memories effectively, and this would explain how memories are "patterns of neural activity". I find this hypothesis of mine necessary considering that the widely accepted science of Synaptic Plasticity fails to explain exactly *what a memory is*, only explaining that memories are stored as a pattern of neural activity—how memories are activated, negated, strengthened, or weakened over time. In my view a single neuron could contain vast amounts of information, and I do believe this hypotheses could merge with ORCH-OR theory, seeing that "consciousness" does not necessarily require memory, but memory requires consciousness.

Engrams will be at some point in time quantifiable through extremely sophisticated imaging technology or brain implants, and copyable / transferable to synthetic brains and servers (cyberspace), leading to what many will consider *immortality*. Although I do not consider the copying and implantation or uploading of engrams to be a transfer of consciousness, as it is instead the creation of a new highly similar artificial or organically-merged consciousness, and therefore not immortality, for even if we are to

describe consciousness in the most rational mechanical sense, as being only the sum of memories (due to environmental waves) and the density and interactivity of neuronal cells, and their respective microtubules, then we can still safely infer that to *transfer* consciousness is impossible, as consciousness exists within the confines of time and space, and within a specific locality of time and space (the total sum of neurons), and therefore to achieve true immortality, religious views aside, would require the prevention of our original, organic-based consciousness from going permanently "*offline*" i.e. to prevent physical, cellular death.



Although an argument may be made that during sleep, we lose consciousness, and during wake we regain consciousness, therefore providing evidence that consciousness transfers, or changes daily, this is technically not true, considering that the brain is always active, even in sleep, hence we dream of source material from previous experiences. The same can be said for comatose individuals, they are not neurologically dead, their memories

and their personalities still exist, but we do not possess the technology as of yet to bring them to full consciousness, and strangely many choose to "pull the plug" on their loved ones out of moral convenience, rather than having hope, and seeking novel scientific ways to free them from their cognitive prisons, although this complacency with death is also surely due to the misinformation on neurological processes that overseeing physicians or specialists provide, who must often consider the comatose individuals as a medical burden, rather than a future medical miracle. I understand that certain people may consider it improper for me to bring up the previous moral quandary, but I do not argue from a place of emotion or religiosity, I argue in line with the impressive science below.

Another argument may be made that engrams already exist in epigenetic inheritance (originally described by Freud as "Phylogenetic Fantasy"), but this is not a transfer of consciousness, it is a transfer (inheritance) of emotionally laden memories. Furthermore, it may be said without citing research that far more memories are made in our lifetime than inherited from our ancestors, although the strength of memories inherited may be greater, such as the power of the physiological drives; libido, hunger, thirst, & sleep, or other mammalian instincts.

In the distant future, the ultrawealthy and influential individuals who have the chance to copy their identities onto engram files will be under the impression that they will live forever by doing so, but likened to a textual autobiography, their *reanimated self's* will only be weak representations—simulacrums of previous human beings, devoid of the original *spark* (action potentials) of life. In the cases of engram transfer to human hosts, that being the possibility of implanting a specific personality and its memories, we must not forget that a human personality comes not only from brain activity, but from its microbiome makeup, meaning that unless the literal "guts" of the diseased immortality seekers are transplanted, their new hosts will be missing something that they will never be able to regain through technology alone.

In the research paper below, the scientists Sheena A. Josselyn and Susumu Tonegawa discuss the history and newest developments of Engram science.

In (1) we learn that neurons compete for allocation and formation of Engrams based on excitability. A neuron with higher excitability means a neuron that produces more action potentials following stimulation.

In (2) we learn that Engram cells display increased synaptic strength (increased AMPA receptor expression (increased AMPA receptor numbers), increased number of synapses, or increased synaptic connections (lengthier axons / dendrites) following learning.

In (3) we learn that Silent Engrams, aptly and topically described by Freud in his theory of "Repressed" memories, are memories that have suppressed reactivation. Silent Engrams are formed because of a disruption in synaptic efficiency (decreased dendritic spine density) leading to decreased communication between neurons, likely due to neurotransmitter imbalances, stress chemicals, or neurodegenerative conditions. Traditional theory suggests that memories formed during learning are capable of being

blocked from storage through protein synthesis inhibition (neurological protein synthesis = the synthesis of neurotransmitter receptors, or synaptic scaffolding proteins, which are similar to costameres in function), but new science suggests the process of memory consolidation is directly related to the process of memory retrieval, meaning that the brain is constantly storing information (memories) even during times of neurological degeneration, or periods of drug-induced "amnesia".

In (3) we also learn Silent Engram neurons are capable of activation through a science called Optogenetics, where genetically modified neurons are capable of being activated through light.

Interestingly, Light-based Neuron activation is likely to be a future therapy for accessing traumatic memories by using Viral Delivery of Light-sensitive Proteins (VDLP) in viral vectors which will alter human neurons to become photosensitive. This Optogenetic therapy will obviously be used for good, such as being used to overcome repressed memories, and bad, such as being used as the most dystopian form of interrogation, and even worse, being used to suppress the activation of memories, to brainwash a population, this being only possible through neural implants.

Introduction

"<>In 1904, Richard Semon introduced the term "engram" to describe the neural substrate for storing memories. An experience, Semon proposed, activates a subset of cells that undergo off-line, persistent chemical and/or physical changes to become an engram. Subsequent reactivation of this engram induces memory retrieval. Although Semon's contributions were largely ignored in his lifetime, new technologies that allow researchers to image and manipulate the brain at the level of individual neurons has reinvigorated engram research. We review recent progress in studying engrams, including an evaluation of evidence for the existence of engrams, the importance of intrinsic excitability and synaptic plasticity in engrams, and the lifetime of an engram. Together, these findings are beginning to define an engram as the basic unit of memory.

<>Memory is the ability to use the past in service of the present or future . Memory is central to our everyday lives and defines who we are. Without it, we are condemned to an eternal present. That memory persists after an experience suggests that an internal representation of this experience is stored in the brain and that later this representation can be reconstructed and used. In 1904, Richard Semon, an evolutionary zoologist turned memory theorist, introduced the term "engram" to describe such memory representations. Semon defined an engram as "…the enduring though primarily latent modifications in the irritable sub-stance produced by a stimulus…". He postulated a fundamental "law of engraphy" in which "all simultaneous excitations… form a connected simultaneous complex of excitations which, as such, act engraphically, that is to say leaves behind it a connected, and to that extent, unified engram-complex". An engram, therefore, is roughly equivalent to a "memory trace."

<>Semon's innovative ideas were largely over-looked or dismissed during his lifetime. However, his theories foreshadowed many prominent contemporary memory concepts. Semon defined an engram as an off-line, physical change in some aspect of brain state

but was suitably cautious when asked to speculate on the precise neural mechanisms underlying an engram, “To follow this into the molecular field seems to me…a hopeless undertaking at the present stage of our knowledge and for my part, I renounce the task”.
<>A few years later, though, Karl Lashley, a geneticist turned psychologist, took up this challenge by systematically attempting to localize an engram in a mammalian brain. In a typical study, Lashley trained rats over many days to solve a maze by running a distinct route to collect a reward. Hypothesizing that some critical component of the engram supporting this maze-route memory is localized in the cortex, Lashley removed cortical tissue of varying sizes from varying locations and then tested the rats’ memory for the maze route. Although the amount of cortical tissue removed correlated with overall memory impairment, the location of the lesion did not. After more than 30 years of searching, Lashley failed to find an engram, declaring it “elusive.”
<>The next leap in engram-related research came when Donald O. Hebb, a psychologist, memory theorist, and student of Lashley, developed a cell assembly theory (similar to Semon’s engram complex). Hebb hypothesized that a cell assembly is formed between reciprocally interconnected cells that are simultaneously active during an experience. Sufficient activity within the cell assembly induces growth and/or metabolic changes that strengthen the connections between these cells [a concept distilled in the phrase “neurons that fire together, wire together”]. These synaptic and metabolic changes (perhaps including changes in intrinsic neuronal excitability) have implications for the function of a cell assembly. For instance, reactivation of only a fraction of assembly cells was hypothesized to produce reactivation of the entire assembly [a process similar to pattern completion]. By contrast, destruction of a fraction of assembly cells would not necessarily produce catastrophic failure of the entire representation (but rather gracefully degrade the representation). Interestingly, Semon also proposed similar types of properties for an engram.
<>Together, these (and other) scientists helped define and describe an engram. However, there was a paucity of studies examining the biological basis of engrams. More than 100 years ago, Semon wrote that to examine the neurobiological basis of an engram represented a “hopeless undertaking.” This may no longer be true. Recent excitement surrounding engram research may stem directly from the development of new tools allowing cell ensembles to be imaged and manipulated at the level of the individual cell.”
“<>It is important to note that an engram is not yet a memory but rather provides the necessary physical conditions for a memory to emerge. Memories are retrieved when appropriate retrieval cues successfully reactivate an engram in a process Semon dubbed “ecphory.”

(1) Birth of an Engram

“<>Josselyn, Silva, and colleagues discovered that during engram formation, eligible neurons in a given brain region compete against each other for allocation (or recruitment) to an engram. Neurons with relatively increased intrinsic excitability win this allocation competition to become engram cells. Competitive excitability-based allocation to an engram occurs in other brain regions and supports different types of memories [e.g.,

dorsal CA1 region of hippocampus and prefrontal cortex (for a contextual fear memory), insular cortex (conditioned taste-aversion memory), and retrosplenial cortex (spatial memory)].

<> In addition to aversive memories, LA neurons experimentally made more excitable during training were also preferentially allocated to an engram supporting a cocaine-cue rewarding memory. Similarly, increasing the excitability of a small, random portion of piriform cortex principal neurons resulted in their allocation to an engram supporting either a rewarding or an aversive olfactory memory, depending on the nature of the training experience. Excitability-based neuronal allocation is predicted by computational modeling, occurs endogenously, and is consistent with previous research implicating intrinsic excitability in the formation of invertebrate memory traces. Together, these findings suggest that in some brain regions, at any given time, a small portion of eligible neurons are "primed" to become part of an engram (should an experience occur), regardless of experience valence.

<>Although stable place cells and engram cells in dorsal CA1 of the hippocampus differ, some mechanisms underlying their formation may be shared. In a given environment, only a small subset of CA1 neurons are place cells, because the majority of CA1 neurons are silent. Those neurons with relatively higher excitability immediately before placement in a novel environment are more likely to become place cells in that environment, and experimentally increasing the excitability of an initially silent cell biased this cell toward becoming a place cell.

<>It is interesting to note the similarities between data from current allocation studies and the long-standing idea of selective stabilization. Selective stabilization proposes that multiple prerepresentations are endogenously generated in the brain and only one or a few that fit the situation are selected at any given point of time to control behavior and/or persist. Both allocation and selective stabilization resonate with the conceptual framework of Darwinian competition.

<>Observational and tagging experimental studies agree with computational theories that an engram is sparsely encoded. That is, not all neurons within a given brain region become an engram cell supporting a particular memory. The size of an engram within a given brain region (that is, the number of engram cells) is stable and invariant to memory strength. For instance, the size of an LA engram (number of LA engram cells) is similar for an auditory fear conditioned memory and a cocaine-cue memory, and memory strength does not affect engram size. Rather, a stronger memory engages a greater number of synapses between engram cells.

<>Several lines of evidence suggest that one mechanism constraining engram size involves inhibitory neurons. Thus, inhibiting parvalbumin-containing interneurons in the basolateral amygdala complex increased the size of an engram in the LA supporting an auditory fear memory through a process involving di-synaptic inhibition, in which an excitatory neuron inhibits another excitatory neuron via an intervening inhibitory neuron. Moreover, inhibiting somatostatin-containing interneurons increased the size of a DG contextual fear memory engram through a lateral-inhibition like process. The importance of inhibitory neurons in engrams has also been highlighted in human studies. For instance, evidence suggests that in the cortex, associative memories are represented in

excitatory engrams and matched (equal and opposite) inhibitory engrams. Memories are expressed upon disinhibition of the excitatory engram. Further exploration of excitatory-inhibitory balance in engram formation, storage, and retrieval is necessary to understand how these opposing forces interact to support memory function."

(2) The "enduring changes" of an Engram

"<>The ability to label in vivo engram cells supporting a specific memory provided an opportunity to investigate the nature of the "enduring changes" proposed by Semon. Guided by Hebb's influential theory on the critical importance of synaptic plasticity (the increase in synaptic strength between neurons) in memory, Tonegawa and colleagues showed that learning augmented synaptic strength, specifically in engram cells. First, 1 day after training, hippocampal DG granule engram cells tagged during contextual fear conditioning showed greater synaptic strength [higher AMPA/NMDA ratio, which is a means of assessing basal strength of excitatory synapses by examining the relative expression of amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR)–mediated synaptic currents to N-methyl-D-aspartate receptor (NMDAR)–mediated synaptic currents of a population of stimulated synapses and increased spine density at entorhinal cortex junctions than nonengram DG cells.
<>Second, compared to nonengram CA3 cells, downstream CA3 engram cells were more functionally connected with upstream DG engram cells. Moreover, Kaang and colleagues showed that the number and sizes of spines on CA1 engram cells tagged during contextual fear conditioning receiving input from CA3 engram cells was greater than on nonengram CA1 cells. This enhanced interregional connectivity between CA3 and CA1 engram cells correlated with memory strength and occluded long-term potentiation (LTP), suggesting a previous LTP-like phenomenon endogenously occurred.
<>Similarly, LA engram cells tagged during auditory fear conditioning showed enhanced synaptic connectivity with presynaptic neurons. Finally, shrinking potentiated synapses in primary motor cortex (M1) engram cells supporting a motor memory disrupted subsequent performance of this, and not a similar, motor memory. Together, these studies are beginning to integrate previous research on synaptic plasticity with engrams and suggest preferential engram cell–to–engram cell connectivity is a critical part of the enduring changes to an engram generated by learning. Overall, these findings suggest an update of Hebb's axiom: Engram cells that fire together, wire together."

(3) Silent Engrams

"<>Engrams may become damaged, such that a memory becomes forever unavailable. However, engrams may also be temporarily inaccessible, such that the engram still exists but cannot be retrieved by natural means. Silent engrams, engrams that cannot be retrieved by natural retrieval cues but can be retrieved with direct optogenetic stimulation, were first revealed in an experiment in which the protein synthesis inhibitor, anisomycin, was administered immediately after contextual fear conditioning in mice. Inhibiting protein synthesis before or immediately after an experience is known to induce

amnesia and block cellular consolidation. Cellular consolidation refers to the relatively fast process of memory stabilization thought to involve the expression of genes necessary to strengthen synapses. By contrast, systems consolidation (discussed below) refers to the slower, time-dependent reorganization of memories over distributed brain circuits.
<>In this study, mice administered anisomycin immediately after training showed little freezing when replaced in the training context 1 day later. Therefore, as expected, disrupting protein synthesis induced retrograde amnesia by blocking cellular consolidation. However, optogenetic reactivation of DG engram neurons tagged during contextual fear training was sufficient for memory recovery, even 8 days after training. These results indicate that the engram was formed and persisted for several days but that this engram could not be retrieved by natural means. Silent DG engram cells showed weaker physiological (increased synaptic strength) and structural (increased dendritic spine density) alterations than normal engram cells (in control mice), suggesting that a silent engram may be the result of disrupting the synaptic strengthening normally induced by training.
<>That optogenetic activation of DG engram cells was able to induce memory retrieval suggests that direct optogenetic activation was able to circumvent this requirement for synaptic and structural plasticity within engram cells. Consistent with this, genetic restoration of spine density [targeted overexpression of p-21 activated kinase (PAK 1)] also allowed a silent engram to be reactivated and memory expressed by natural retrieval cues.
<>The idea that engrams may be silenced by disrupting synaptic efficacy and spine density and reawakened by enhancing synaptic plasticity is consistent with findings from a nonengram study examining auditory fear conditioning. Rats were trained in a variant of an auditory fear conditioning task in which the tone conditioned stimulus was replaced by optogenetic activation of LA axon terminals from neurons originating in the medial geniculate nucleus and auditory cortex. Immediately after conditioning, long-term depression (LTD)–like optogenetic stimulation was administered. LTD is thought to weaken synaptic efficacy and decrease spine density. <>Consistent with the interpretation that LTD-like stimulation silenced the engram, this opto-LTD stimulation im-paired subsequent memory recall. However, LTP-like optogenetic stimulation allowed the memory to be retrieved (consistent with the interpretation that the engram was "unsilenced"). Again, subsequent LTD-like optogenetic stimulation silenced this memory, whereas LTP-like optogenetic stimulation allowed recovery of this memory.
<>These findings raise the question of whether engrams (and the memories they support) in other amnesic conditions are truly "lost" or are simply inaccessible such that they cannot be retrieved under natural conditions. Silent engrams were reactivated by artificially stimulating engram cells in amnestic mice used to study the early stages of Alzheimer's disease (AD). These transgenic mice [APP/PS1 mice containing human transgenes with the familial AD mutation in both amyloid precursor protein (APP) and presenilin 1 (PSEN1)] showed contextual fear memory deficits. However, optogenetic reactivation of ChR2-labeled DG engram cells induced robust freezing comparable to control mice. Consistent with other examples of silent engram cells, DG engram cells in these mice used to study AD showed decreased spine density. However, LTP-like

optogenetic stimulation at entorhinal cortex engram cell inputs onto DG engram cells restored not only spine density in DG engram cells but also the ability of natural retrieval cues to elicit memory retrieval (thereby unsilencing the engram).
<>These findings in mice are consistent with reports that memory retrieval in people with early-stage AD may be enhanced by particular retrieval cues. Therefore, under certain conditions, a previously inaccessible memory may be retrieved in human AD, consistent with the interpretation that some engrams in early-AD brains may be silent rather than lost.
<>Apart from clinical implications, the finding of silent engrams is relevant to discussions on the role of protein synthesis–dependent cellular consolidation in terms of memory storage versus retrieval. There has been persistent debate on this issue. The majority of neuroscientists examining cellular memory consolidation may favor the view that disrupting protein synthesis disrupts memory storage. However, in many amnesia experiments, memory storage is conflated with memory retrieval. The finding that optogenetically stimulating a silent engram in an otherwise amnestic mouse, even 1 week after training, induces memory retrieval challenges the view that protein synthesis–dependent cellular consolidation is important for memory storage. <>Instead, these findings suggest that the role of cellular consolidation is to enhance subsequent retrievability of an engram, consistent with the idea of engram "retrieval handles" that are established after memory formation and may be remodeled after memory retrieval. Importantly, silent engrams are consistent with the pioneering cognitive psychologist Endel Tulving's conceptual distinction between memory availability and accessibility, in which memory failure may reflect the absence of the information or difficulties accessing the information."[85.A]

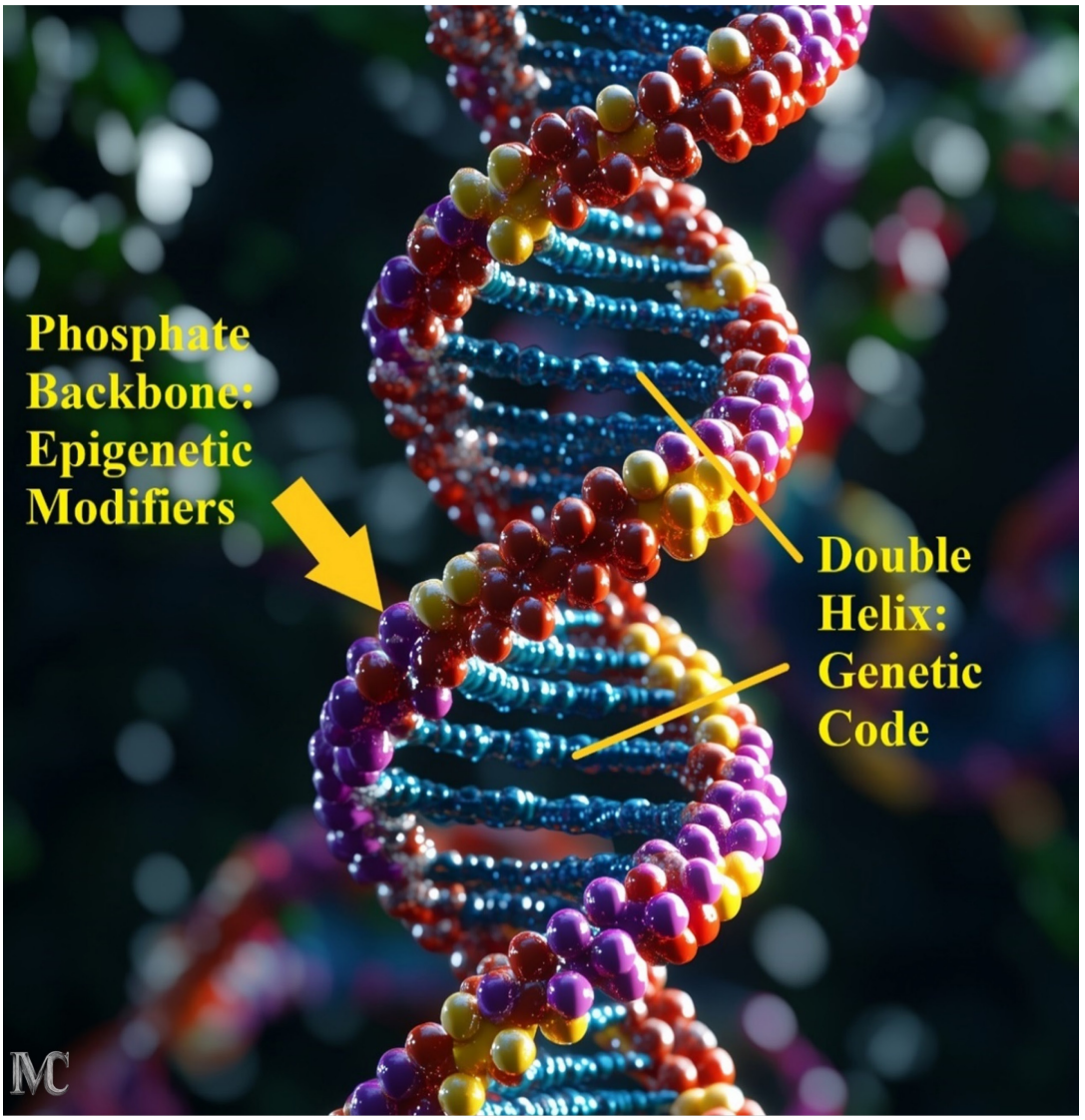
[See: IMC Sciences Overview: The Cornu Ammonis (CA) areas of the brain]

Myogenic Epigenetic Inheritance

Genetic information is passed down through genetic information stored in the helix's of DNA strands, the strength of these genes are controlled by the phosphate backbones which contain epigenetic modifiers, that enhance of silence gene expression.
There are two types of inherited behaviors, the primary is Epigenetic Inheritance, where environmental factors change the DNA of parents, which is passed down to their offspring. The second and more interesting phenomenon of inheritance is *Phylogenetic Fantasy* which describes brain memory inheritance (instincts, behaviors, desires, etc.) from parent to offspring, and this was hypothesized by Sigmund Freud, in which he posited that psychological trauma is inherited from one generation to the next [Read: Moses & Monotheism: "Phylogenetic fantasy". Published in 1939, long before certain 21st Century overzealous collegiate researchers claimed to have created this theory].

Phylogenetic Fantasies were originally discovered by ancient religious thinkers from India who created the idea of *Reincarnation*, referred to as Samsara, a supremely

impressive biomedical-religious discovery made 2500-3000 years ago. Humans do inherit certain fear memories from their parents, and this may be confused as evidence for reincarnation. It is very dangerous to suggest all moral burdens are inherited from one generation to the next, but it is logical to now say certain memories are inherited from one generation to the next. Reincarnation is regardless an impressive semi-scientifically accurate ancient explanation of the appearance and facilitation of certain inherited human behaviors, behaviors that are only activated when an offspring encounters special environmental factors (cues) that are necessary to trigger the activation of one or more specialized genes.



Some readers may consider me to be insane to suggest the existence of both phylogenetic and epigenetic memories, but I ask you this, how does a bird that has only recently fledged know how to forage, fly, and eventually mate, is it really just a “genetic

predisposition" combined with visual mimicry, or is it unconscious memories stored in every cell in their bodies inherited from generations of ancestors. And, yes, birds possess an unconscious mind and have been shown to dream and experience REM sleep.

The question is; is there such a thing as epigenetic myogenic inheritance, are the children of elite athletes more responsive to training stimulus than the uninitiated? Aside from being raised under the variables of a certain work ethic and diet (the strictures required for maximal neuromuscular performance), if fear memories are able to pass down from one generation to the next, it could then be possible to transmit motor pathway memories. It is quite clear that a vast number of elite athletes have a genetic advantage, such as alterations to the PPARGC1A gene (PGC1a), EPOR gene (Erythropoietin: Red Blood Cell Production Stimulator), or ACE (I)/(D) gene deviation (Blood pressure control / IGF-1 Release). It must also be possible too that we are capable of passing down increased myonuclei accretion rates, lipolytic programming potential, or motor memories to our children. Regardless, we often forget that we actively epigenetically modify our children, such as when a pregnant mother chooses to consume or not to consume vitamins during pregnancy, or she chooses to use drugs, the growth of the babies brain and muscle tissue is surely not only dependent on the dietary composition of macronutrients and predetermined genetics, but the variegated environmental factors, especially those willingly absorbed.

[A] Mice of a smaller Litter-size (i.e., greater access to food in early life) promotes obesity & liver damage, and the offspring of these mice also developed liver damage.

"<>Childhood obesity increases the risk of developing metabolic syndrome later in life. Moreover, metabolic dysfunction may be inherited into the following generation through non-genomic mechanisms, with epigenetics as a plausible candidate. The pathways involved in the development of metabolic dysfunction across generations in the context of childhood obesity remain largely unexplored. We have developed a mouse model of early adiposity by reducing litter size at birth (small litter group, SL: 4 pups/dam; control group, C: 8 pups/dam). Mice raised in small litters (SL) developed obesity, insulin resistance and hepatic steatosis with aging.
<>Strikingly, the offspring of SL males (SL-F1) also developed hepatic steatosis. Paternal transmission of an environmentally induced phenotype strongly suggests epigenetic inheritance. We analyzed the hepatic transcriptome in C-F1 and SL-F1 mice to identify pathways involved in the development of hepatic steatosis. We found that the circadian rhythm and lipid metabolic process were the ontologies with highest significance in the liver of SL-F1 mice.
<>We explored whether DNA methylation and small non-coding RNAs might be involved in mediating intergenerational effects. Sperm DNA methylation was largely altered in SL mice. However, these changes did not correlate with the hepatic transcriptome. Next, we analyzed small non-coding RNA content in the testes of mice from the parental generation. Two miRNAs (miR-457 and miR-201) appeared differentially expressed in the testes of SL-F0 mice. They are known to be expressed in

mature spermatozoa, but not in oocytes nor early embryos, and they may regulate the transcription of lipogenic genes, but not clock genes, in hepatocytes. Hence, they are strong candidates to mediate the inheritance of adult hepatic steatosis in our murine model.
<>In conclusion, litter size reduction leads to intergenerational effects through non-genomic mechanisms. In our model, DNA methylation does not seem to play a role on the circadian rhythm nor lipid genes. However, at least two paternal miRNAs might influence the expression of a few lipid-related genes in the first-generation offspring, F1."[85.0]

[B] Fear memories associated with odors are passed down to offspring through epigenetic inheritance.

"<>In one study, male mice were fear conditioned with an odorant at two months of age (post-puberty but not yet adults). The odorant acetophenone paired with an electric shock resulted in behavioral sensitivity in the fear conditioned mice, with an accompanying change in DNA methylation in brain and sperm of the M71 receptor, which is involved in sensing acetophenone. An increased size in the M71 specific glomeruli in the olfactory epithelium and bulb was also observed. The offspring (F1) of odor conditioned F0 males mated with naïve females also showed similar changes in brain and sperm. When the F1 males were themselves mated, changes in brain persisted in the F2 male offspring."[85.1]

[C] Psychological stress and its resultant change to behavior is passed down to offspring through epigenetic inheritance.

"<>Two groups of male mice were exposed to a wide range of stressors over 42 days at puberty or adulthood. These mice (F0) demonstrated behavioral changes in response to the stressor, and also changes in several specific sperm microRNA. Males were bred with naïve females and produced offspring with blunted HPA axis responsivity as well as changes in transcription of GR genes in the paraventricular nucleus.
<>These findings confirmed that early or later life exposures in the male mouse can affect germ cell microRNA, and are sufficient to result in a similar phenotype in the subsequent generation, again confirming the transmission through sperm in an independent animal model. This study is noteworthy for examining both male and female F1. Although significant sex differences were noted in endocrine and behavioral measures, there was no interaction between sex and paternal stress in the offspring of those exposed at puberty or adulthood.
<>An independent research team also demonstrated that small non-coding RNAs (sncRNAs), common in sperm, can mediate inheritance of environmentally acquired traits or phenotypes in mice. Specifically, early life stress, modeled by unpredictable maternal separation and maternal stress, led to depressive-like behavioral patterns upon exposure to novel environments and changes in sncRNAs in F1 sperm. F0 exposed to several unpredictable maternal stressors and separation demonstrated changes that could be observed across two generations176. When altered microRNAs from sperm of the

stressed males were injected into fertilized wild-type oocytes, comparable behavioral, metabolic and molecular outcomes were observed in the F2 offspring, indicating transmission of epigenetic marks. Furthermore, F3 offspring of these animals continued to show phenotypic differences, indicating conservation of stress effects through sperm. <>Importantly, another study demonstrated that environmental enrichment following stress exposure in the F0 could reverse and prevent some of the effects. Early maternal separation resulted in decreased nr3c1 DNA methylation in the hippocampus and sperm cells, as well as poor coping behavior. When environmental enrichment was applied at weaning until adulthood, the behavioral and methylation effects were no longer observed in the F0 or F1. These findings indicate that stress-induced changes to germ cells are not immutable and can be reversed by alternative environmental perturbations that are directed at stimulating plasticity. It is for this reason that environmental effects which cross the generations do not necessarily predict negative generational consequences – posing challenges for interpretation of such effects."[85.2]

[D] Heart transplant receivers are known to experience changes in personality post-surgery 1.

"<>Personality changes following heart transplantation, which have been reported for decades, include accounts of recipients acquiring the personality characteristics of their donor. Four categories of personality changes are discussed in this article: (1) changes in preferences, (2) alterations in emotions/temperament, (3) modifications of identity, and (4) memories from the donor's life. The acquisition of donor personality characteristics by recipients following heart transplantation is hypothesized to occur via the transfer of cellular memory, and four types of cellular memory are presented: (1) epigenetic memory, (2) DNA memory, (3) RNA memory, and (4) protein memory. <>Other possibilities, such as the transfer of memory via intracardiac neurological memory and energetic memory, are discussed as well. Implications for the future of heart transplantation are explored including the importance of reexamining our current definition of death, studying how the transfer of memories might affect the integration of a donated heart, determining whether memories can be transferred via the transplantation of other organs, and investigating which types of information can be transferred via heart transplantation. Further research is recommended."[85.3]

[D2] Heart transplant receivers are known to experience changes in personality post-surgery 2.
"<>Heart transplantation is not simply a question of replacing an organ that no longer functions. The heart is often seen as source of love, emotions, and focus of personality traits. To gain insight into the problem of whether transplant patients themselves feel a change in personality after having received a donor heart, 47 patients who were transplanted over a period of 2 years in Vienna, Austria, were asked for an interview. Three groups of patients could be identified: 79% stated that their personality had not changed at all postoperatively.

<>In this group, patients showed massive defense and denial reactions, mainly by rapidly changing the subject or making the question ridiculous. Fifteen per cent stated that their personality had indeed changed, but not because of the donor organ, but due to the life-threatening event. Six per cent (three patients) reported a distinct change of personality due to their new hearts. These incorporation fantasies forced them to change feelings and reactions and accept those of the donor. Verbatim statements of these heart transplant recipients show that there seem to be severe problems regarding graft incorporation, which are based on the age-old idea of the heart as a centre that houses feelings and forms the personality."[85.4]

Eugenics, Cloning, & Chimeras

CRISPR-Cas systems originally come from bacterial immune systems, where snippets of virus DNA are saved post-infection for better defense against reinfection. From studying Bacterial CRISPR-Cas systems scientists have created the biotechnology called CRISPR-Cas9, which allows them to "cut" DNA out and add new DNA templates, to therefore edit genes.

Eugenics

Genome editing will play an integral role in human procreation, especially in totalitarian nations, such as China, where there exists no popular religion to give pause to the technological advancements that will defile inherited moralities. Through using the genome editing technology CRISPR-cas9, parents will be able to change the genetics of their children by altering their embryos, to make them smarter, faster, stronger, or instill certain skills into them when they reach maturity. No doubt these technologies will cost exorbitant sums of money and thus be only available to the richest future parents in society.

Interestingly, it is unlikely that in the distant future every citizen will be genetically modified before birth mandatorily by the government, because there will always be a class stratification, and the poor and sickly will not have genetics considered worthy of offspring modification.

The children who have been modified will outperform their more natural, hardworking contemporaries, and will overtake all STEM jobs, and nearly all high paying jobs, but their enhanced physical and mental abilities will come at suppression of free will, for they will be designed and conditioned to do a certain job, or to excel at a certain skill, to be made of only *desirable traits* and ironically this was quite literally the dream of Josef Mengele, a high ranking Nazi official.

Eugenics is in fact already popular among society in the form of *Selective Breeding*, in that fetuses screened through testing and showing a positive risk for down syndrome development are aborted at a much higher rate, which raises an enormous ethical issue, for to end the life of a fetus that will in all likelihood develop down syndrome is nothing

more than to selfishly eliminate the possibility of undertaking an "*unnecessary*" inconvenience that most parents do not wish to undertake, for there is no other excuse to end the life of a down syndrome fetus, except the fact that taking care of them will be difficult. But we must remember a child with down syndrome still experiences consciousness, and emotion, and therefore likened to Hitlers hate towards disabled individuals, parents that abort fetuses that may develop down syndrome are engaging in not only selective breeding, but *eugenics-against-disability*, which are in my opinion morally reprehensible acts far worse than unintended pregnancy abortions, or the future—eugenics through modification. But in a society where technology becomes god, or where we consider ourselves as gods, a new morality comes into being—a *grey* moral quiescence.

Countries such as Iceland, and Denmark have extremely high abortion rates of close to **95%** for babies that have gone through prenatal genetic testing (screening) and were shown to have a high risk of developing down syndrome, and this trend is increasing in many other countries (it's around **70%** in the USA). Take note of this article from CBS news:

"<>With the rise of prenatal screening tests across Europe and the United States, the number of babies born with Down syndrome has significantly decreased, but few countries have come as close to eradicating Down syndrome births as Iceland.
Since prenatal screening tests were introduced in Iceland in the early 2000s, the vast majority of women -- close to 100 percent -- who received a positive test for Down syndrome terminated their pregnancy.
While the tests are optional, the government states that all expectant mothers must be informed about availability of screening tests, which reveal the likelihood of a child being born with Down syndrome. Around 80 to 85 percent of pregnant women choose to take the prenatal screening test, according to Landspitali University Hospital in Reykjavik.
<>Geneticist Kari Stefansson is the founder of deCODE Genetics, a company that has studied nearly the entire Icelandic population's genomes. He has a unique perspective on the advancement of medical technology. "My understanding is that we have basically eradicated, almost, Down syndrome from our society -- that there is hardly ever a child with Down syndrome in Iceland anymore," he said.
<>Quijano asked Stefansson, "What does the 100 percent termination rate, you think, reflect about Icelandic society?"
"It reflects a relatively heavy-handed genetic counseling," he said. "And I don't think that heavy-handed genetic counseling is desirable. … You're having impact on decisions that are not medical, in a way."
Stefansson noted, "I don't think there's anything wrong with aspiring to have healthy children, but how far we should go in seeking those goals is a fairly complicated decision."
<>Over at Landspitali University Hospital, Helga Sol Olafsdottir counsels women who have a pregnancy with a chromosomal abnormality. They speak to her when deciding whether to continue or end their pregnancies. Olafsdottir tells women who are wrestling

with the decision or feelings of guilt: "This is your life — you have the right to choose how your life will look like."
<>She showed Quijano a prayer card inscribed with the date and tiny footprints of a fetus that was terminated.
Quijano noted, "In America, I think some people would be confused about people calling this 'our child,' saying a prayer or saying goodbye or having a priest come in -- because to them abortion is murder."
<>Olafsdottir responded, "We don't look at abortion as a murder. We look at it as a thing that we ended. We ended a possible life that may have had a huge complication... preventing suffering for the child and for the family. And I think that is more right than seeing it as a murder -- that's so black and white. Life isn't black and white. Life is grey."”[85.4.1]

Cloning

In terms of cloning technology, it is plausible that this technology is released onto the world at a much later stage in our technological development, long after modification through eugenics becomes popular, because the upper echelons of society will not embrace the thought of multiple versions of themselves running around, as this would create competition in the pecking order, whereas the creation and transfer of engrams identity files will give them a false sense of immortality.

Nevertheless, at some point, all technology is released upon mankind, and cloning will be no different. It would be too easy to suggest that cloning will be a tool used by Totalitarian Governments to create never-ending supplies of soldiers formed of genes that have already been modified through genetic engineering, as despots will likely hoard the technology to simply continue their genetic lineage.

It is instead more probable cloning will be embraced early by middle-upper class barren or homosexual parents, or single parents who will choose to clone one or both of themselves due to being unable to give birth to a child, and this in turn will normalize the technology among all other strata’s of society. I think it possible too that institutions will have the genome of famous celebrities, and that parents will be able to effectively make their children in the superficial image of their favorite entertainers, thus solidifying a future of genomic vapidity.

In this prescient paper titled “The Immorality of Cloning” Daniel R. Heimbach predicts, quite accurately I think, the future moral issues that will arise when cloning technology is embraced by societies, and mirrors most of my logical predictions regarding this future technology:

<u>Health Risks</u>

“<>One category of obvious danger is the hazard that human cloning creates for human health and welfare. While this risk cannot be exactly measured in advance, that such dangers exist is surely beyond doubt. By reducing diversity in the human gene pool, cloning will weaken a natural barrier that helps protect human bodies from attack by

infectious diseases (like malaria) which constantly mutate to find vulnerabilities in the host. As David Stipp puts it, "without sex, we'd soon be toast for germs. " Stipp's expression may be exaggerated, but he identifies a serious issue. The risk to clones from mutating infectious diseases will grow over time. That is, a group of clones will be more likely to die out from a single disease than a comparable group of persons who possess a more random distribution of genes. This danger is even more significant when the corporate impact is added to the risk for individuals. Cloning will make the entire human race more vulnerable to mutating infectious diseases, and the size of this danger will grow exponentially in relation to the rate at which human cloning actually reduces diversity in the gene pool for the race as a whole.

<>Other risks that cloning may pose to human health are raised by questions about cell aging and increased vulnerability to the possibility of birth defects. Many health risks, like the risk of cancer, increase with biological age. Will the genes of a clone continue on the same age trajectory as genes in the body from which they were taken? Or will the genes of cloned cells behave in a regenerated manner despite the age of their DNA arrangement? If genes of cloned cells do not perform in a fully regenerated manner, a clonally generated baby may not have long to live and could suffer degenerative conditions prematurely.

<>Human cloning could also increase the risk of birth defects if cloned individuals begin marrying nearly identical genetic relatives, a danger that will be hard to avoid in second and third generations. Of course, it is important that we not overstate the case by exaggerating health risks associated with human cloning. The point here is not to raise alarm, but simply to recognize that legitimate reasons for concern do exist, and they are not insignificant. Even if risk to human health is the only danger associated with cloning human life, it would at least warrant delay until more can be learned from animal research. Alone, risk to human health may not be sufficient to warrant a permanent ban. But this is not the only danger."

Socio-Political Risks

"<>A second danger posed by human cloning involves risks that are social or political in nature. These are risks having to do with misuse should human cloning ever fall into the wrong hands. Indeed, the danger of misuse is already well-publicized, since the idea of misused human cloning gripped the imagination of science-fiction writers long before it ever became scientifically possible. Crazed scientists could try to combine cloning technology with genetic engineering to generate humanoid monsters such as Mary Shelley's Frankenstein." Criminals could create doppelgangers, or they could use cloning to produce duplications of themselves so exact they would be able to throw detectives off their trails by using cloned identities to establish a basis for plausible deniability. Dictators could try to immortalize themselves or may try to raise an army of "terminators" with which to conquer the world. Finally, social engineers with maniacal dreams could seek total authoritarian control by using reproductive oppression and mass cloning on a scale similar to

the brave new world Aldous Huxley imagined.
<>Such dangers are not trivial just because they were first imagined by writers of science-fiction; and, now that Ian Wilmut has proven it is possible to clone adult mammals, they are no longer impossibly fictitious. More than any other danger associated with cloning humans, the danger of misuse should help us comprehend the importance of erecting reliable safeguards well before anyone ventures into such territory. Again, more than any other danger associated with cloning humans, the enormously negative consequences of misuse show where the burden of proof must lie when political and legal decisions are debated concerning the valuation of human cloning. In fact, the danger of misuse is so large and readily comprehended that no further explanation is needed to expose the foolishness of delaying decision on a ban. A ban is needed immediately, and the burden of proof must be on those who think it unnecessary, not on those satisfied with conditions already free of the dangers human cloning will introduce."

Moral Risks

"<>A third danger, less well considered but perhaps most threatening of all, is the way cloning humans will provoke a variety of immoral consequences. I turn here to the danger of immoral effects likely to arise even if protections are in place to guard against the risk to human health and the danger of misuse. Immoral consequences provoked by human cloning can be divided into four subcategories: (1) trivialization of human worth and dignity; (2) erosion of human freedom; (3) new opportunity for invidious discrimination; and (4) commercialization of human life. The first immoral consequence is the trivialization of human worth and dignity. Such trivializing is immoral because it involves attitudes that regard human beings as less significant, less meaningful, and therefore less worthy of respectful treatment than they are in fact due as human beings.
<>Human cloning, if permitted, raises the specter of trivialized worth and dignity by diminishing the value we recognize in individuals and perhaps confusing (at least in perception) the meaning and significance of human selfhood. Both are pillars of moral valuation essential to a civilized social order. 5 While some may argue that clonal production of human life will be no more hazardous to individuality and selfhood than the natural birth of identical twins, this issue focuses not on twins as they presently occur but on the impact a radical rise in the number of genetically identical persons will have on public thinking. It arises out of the heretofore unprecedented possibility of salting the human race with large numbers of people each genetically identical to persons who have lived before-persons with pre-established histories, reputations, and followings.
<>Beyond the threat of identity confusion, human cloning will threaten to trivialize human worth and dignity in other, more ominous ways. Many already discuss the idea that cloning might offer parents grieving a lost child the possibility of "replacing" that child by producing a clone from a cell obtained from the deceased. Trivialized valuation of human life is also present in the idea that clones could be a source of replacement body parts when age or accident damages components of the human original. Interest in these ideas is ominous because it demonstrates a willingness to lower moral objections against

treating human beings as means rather than ends. They reveal pressures that toleration of human cloning will inspire, pressures that will seek policies and laws allowing non-volitional, instrumental, and detrimental (hence immoral) use of one segment of the race for goals or desires set by or serving the benefit of persons other than themselves.
<>The second immoral consequence is the erosion of human freedom. Cloning technology will tempt scientists and politicians to manage or shape the human gene pool. Experts in human biology and political officials will be attracted to the possibility of breeding for the purpose of multiplying desired strains of human life. But the temptation to do so runs exactly contrary to, and hence threatens, basic human freedom. Even if it is never fully realized, just having the possibility within reach will make the idea of cloning humans "familiar." Then it will begin to look more and more "reasonable."
<>Finally, scientists will try to persuade politicians that cloning without their expert control is "irresponsible," so managing the gene pool will then look very "necessary." Real dangers will be identified and used to direct attention away from opposing dangers caused by putting human reproduction under regulatory government control. Should this happen, it could not take place without overriding many moral principles, obligations, and rights that ought to be respected as inalienable-the individual freedom and personal obligations of self-reproduction; the sanctity and primacy of the family over the state in matters of human reproduction; the responsibility of begetter for the begotten; and the sanctity, independence, and privacy of reproductive decisions."

↓ continued

Cloning Is an Act of Species Suicide

"<>First, human cloning is inherently immoral because it is an act of species suicide. The issue here is not that cloning humans, once allowed, will immediately cause the human race to cease existing. Nor does it mean that cloning will in the end terminate all succession of human life. At issue is the fact that, however gradual, the self-modifying effect of cloning must inevitably produce changes so radical that their accumulation can only be classified as species suicide. This concern was argued by Ramsey who explained that terminating life succession is not the only form of species suicide. Replacement of a species "by a species of life deemed more desirable" falls in the same moral category because it entails "the inner motive and action of any suicide.
<>What clonal self-production would produce over time cannot be the human race we have. At least, it cannot be the sort of human race we have been from creation (or however inception of our race is conceived) until now. Rather, it would be a biologically modified successor to our race, a differently made-up human race-different, not just in time, size, and individual membership, but different in biological constitution. Because clonal reproduction directs the human race toward species replacement, the clonal reproduction of human beings is a form of species suicide, and, because it is a form of suicide, it is immoral for all the reasons that render any act of self-murder immoral." [85.4.2] [Truncated]

[A] Interestingly, we must remember we are more than genes, as our environment, choices, and relationships with people irrevocably change us from infancy to adulthood, therefore clones will never be exact copies of the individuals they originate from (even with epigenetic inheritance), similar to Engram Identity copies. Cloning also appears to carry a high risk spontaneous abortion and genetic mutations in cloned organisms.

"<>Can a human individual be cloned? The correct answer is, strictly speaking, no. What is cloned are the genes, not the individual, the genotype, not the phenotype. The technical obstacles are immense even for cloning a human's genotype.
<>Ian Wilmut, the British scientist who directed the cloning project, succeeded with Dolly only after 270 trials. The rate of success for cloning mammals has notably increased over the years without ever reaching 100%. The animals presently cloned include mice, rats, goats, sheep, cows, pigs, horses, and other mammals. The great majority of pregnancies end in spontaneous abortion. Moreover, as Wilmut noted, in many cases, the death of the fetus occurs close to term, with devastating economic, health, and emotional consequences in the case of humans.
<>In mammals, in general, the animals produced by cloning suffer from serious health handicaps, among others, gross obesity, early death, distorted limbs, and dysfunctional immune systems and organs, including liver and kidneys, and other mishaps. Even Dolly had to be euthanized early in 2003, after only 6 y of life, because her health was rapidly decaying, including progressive lung disease and arthritis."[85.4.3]

[B] Gene editing may unintentionally create new forms of cancers. In this study CRISPR-Cas9 was used to disrupt the mdig gene in test cells, however newly spliced mdig messenger RNAs were created in the process. This leads to alternative splicing, a term that describes different exons joining together. Exons are coding regions of genes; they contain the information necessary for synthesizing proteins. These alternatively spliced mdig mRNA may have oncogenic (pro-cancer) properties by producing new proteins.

"The technique of CRISPR-Cas9 gene editing has been widely used to specifically delete the selected target genes through generating double strand breaks (DSBs) and inducing insertion and/or deletion (indel) of the genomic DNAs in the cells. We recently applied this technique to disrupt mineral dust-induced gene (mdig), a potential oncogene as previously reported, by single guide RNA (sgRNA) targeting the third exon of mdig gene in several cell types, including human bronchial epithelial cell line BEAS-2B, lung cancer cell line A549, and human triple negative breast cancer cell line MDA-MB-231 cells. In addition to the successful knockout of mdig gene in these cells, we unexpectedly noted generation of several alternatively spliced mdig mRNAs. Amplification of the mdig mRNAs during the screening of knockout clones by reverse transcription-polymerase chain reaction (RT-PCR) and the subsequent sanger sequencing of DNA revealed deletion and alternative splicing of mdig mRNAs induced by CRISPR-Cas9 gene editing. The most common deletions include nine and twenty-four nucleotides deletion around the DSBs. In addition, interestingly, some mdig mRNAs showed skipping of the entire exon 3, or alternative splicing between exon 2 and exon 8 using the new donor and accept

splicing sites, leading to deletion of exons 3, 4, 5, 6, and 7. Accordingly, cautions should be taken when using CRISPR-Cas9 strategy to edit human genes due to the unintended alterative splicing of the target mRNAs. It is very likely that new proteins, some of which may be highly oncogenic, may be generated from CRISPR-Cas9 gene editing."[85.4.4]

Human-animal Chimeras

In this strange and shocking paper by the researchers Rodolphe Bourret, Eric Martinez, François Vialla, Chloé Giquel, Aurélie Thonnat-Marin, and John De Voscorresponding on human-animal chimeras and "interspecies blastocyst complementation", where animal embryos are genetically modified with human DNA and are used to grow human organs, to be then harvested at a certain age for transplantation. These researchers discuss the possibility of human-like consciousness developing as being unlikely although they admit *human neural cells are capable of populating an animals brain*, and how genetically modified animals may even develop human facial features, or human body parts, discussing ways to prevent (likely unsuccessfully) all the aforementioned complexities in the coming future of human-animal chimera scientific development.

If it is possible to create animals that grow human organs, can possess human features, and contain human neurons in their brains, it is only a matter of time before we have pets that can think similarly to us. For some this thought may seem exhilarating, but to others, such as myself, it is truly disturbing to think of confining a human-like consciousness and intelligence to the body of an animal as this would be a strange and torturous biomedically enacted evil. It is ominous how some scientists seek to, and eventually will succeed in promoting a regression in our evolution, bringing us back to the time where we crawled on all four limbs, but such is the circle of life.

Background

"The idea of chimeras can be traced back to Antiquity. In Greek mythology the Minotaur had a man's body and a bull's head, and Pan was half man, half goat. Similarly, many Egyptian gods had a human body and a beast head, such as Sobek, Anubis, and Horus. The concept of "chimera" has gone through a semantic shift since Antiquity. Originally, "Chimera" was a proper noun designating a fabulous creature, whereas in modern medicine "chimera" describes a living organism that contains cells or tissues with different genotypes. Nevertheless, there are variations to the exact meaning of this word, depending on the field. In embryology, "chimera" refers to a combination of cells from different individuals. In molecular genetics, "chimera" describes the combination of two DNA molecules from different individuals, or from different chromosomes of the same individual. Conversely, in genetics, "chimera" refers to interspecies hybrids, such as the mule (the cross of a female horse with a male donkey). "Chimera" may even refer to the grafting in a postimplantation embryo of cells or tissues from another individual or species, such as the injection of hematopoietic stem cells intraperitoneally into a sheep fetus to produce a chimeric sheep that expresses human myeloid and lymphoid lineages. In the rest of this article, "chimera" will refer to the meaning used in embryology."

Human-like consciousness

"<>It is our brain that makes us humans. Therefore, it is crucial to determine whether injection of human iPSC into animal blastocysts could humanize the animal brain. Specifically, could a significant contribution of human cells to the animal brain modify the characteristics of the recipient species? Would this affect the evaluation of the moral status of the animal, especially in the case of large animals, such as pigs and particularly nonhuman primates? Indeed, if the presence of human cells in the animal brain resulted in a form of human-like consciousness, such scientific experiments would become ethically unacceptable because a major distinction between humans and animals is based on consciousness.

<>Surely, if chimeric animals were to acquire a human-like consciousness, it would be necessary to treat them as humans and consequently any form of organ culture would be prohibited. However, this is very unlikely. As discussed by Karpowicz et al., neural progenitor cells need more time to develop and go through many more divisions and result in a larger brain in primates than in most other animals. Hence, the formation of a large human-like brain within the time and space limits imposed by a nonhuman host is highly improbable. For example, the sow's gestation period is approximately 3 months, one-third of a human pregnancy and far shorter than that of extremely preterm babies. Therefore, even if human neural progenitors would take over, the timeframe of a saw's gestation would not be long enough to allow the full development of the neural structures needed to give rise to human functions and behaviors.

<>Nevertheless, there are several ways to limit this risk. First, iPSC should be injected only for complementation. In this setting, human cells would mostly replace cells/tissues that are absent as a consequence of gene knockout, as done in the Pdx1–/– mice. Human cells are expected to be less competitive than pig cells in a pig microenvironment, unless a specific pig cell type has been impaired by genetic means. This considerably limits the risk of significant animal brain colonization by human cells. Nevertheless, certain human cell types may have an intrinsic competitive advantage over animal cells, particularly in the brain, and this can raise concerns. This was shown recently by injecting human glial progenitor cells into immunodeficient neonate mice. Human glial progenitor cells outcompeted mouse glial progenitor cells and ultimately, in these mice, the white matter was largely of human origin. Strikingly, engraftment of human glial progenitor cells enhances synaptic plasticity and learning in adult mice.

<>To prevent the worst-case scenario of a humanized pig brain, it will be mandatory to define a maximal limit of human chimerism in the pig brain that cannot be exceeded. To this aim, brain chimerism could be assessed in a significant number of chimeric animals sacrificed at different time points during gestation and then after birth at different ages. Moreover, the injected human iPSC could be genetically modified to render them incapable of differentiating into neural cells, or could include "suicide genes" that would only be activated upon neural differentiation. Finally, a most recent proposition is the forced expression of the MIXL1 gene that forces cells into a visceral fate, thus avoiding the danger of neural differentiation."

Human-like external features

"<>It may be argued that the injection of human iPSC into animal embryos could have an effect on the physical aspect of the animal; in other words, on its appearance. The creation of human/animal chimeras can make the boundary between human beings and other living beings porous, inducing questions about our human identity. These interrogations and concerns are more obvious when it comes to a chimera whose physical attributes would let its chimeric quality explicitly appear. It must be said that our moral intuition is particularly influenced by identity attributes. Thus, in a report related to human/animal chimeras, the German Ethics Committee considered that "aspects of the visible form of a living organism that are considered, in particular, to be relevant to identity, may strongly influence their intuitive ontological classification". It is not only about the creature's appearance, but also about its specific attributes, such as language. <>Previous studies concluded that the donor cell contribution is almost 20 % in rat–mouse chimeras. This is less important than in allogeneic (mouse–mouse) chimeras where it is estimated at 50 %. On the basis of these observations, researchers hypothesize that the contribution of human cells injected into pig blastocysts should be lower than 1 %. Therefore, the risk of seeing the birth of pigs with human features is expected to be very low. Here again, a maximum threshold of human cell contribution should be established beforehand and strictly implemented. This risk could be further limited by performing a prebirth systematic diagnosis to detect the presence of human features. If, for instance, a pig embryo had a hand or a foot, it would be sacrificed. Ultimately, only fetuses without any human feature would be allowed to term."[85.4.5]

Sleep

Sleep is the most essential and natural process for memory encoding. Sleep is controlled by the Circadian Rhythm, which is a complex cellular process composed the Suprachiasmatic Nucleus (SCN) and certain "Clock Genes". When light enters into the eyes, or there is a lack of light entering into the eyes, the SCN interprets these light signals to regulate hormone release, such as light-induced (daytime) cortisol release, and darkness-induced (nighttime) melatonin release. Cleary one of the major downsides of our technological future is the chronic blue light exposure we are exposed to from staring at digital screens that disturb our circadian rhythm.

NMDA receptors facilitate sleep, alongside Melatonin, Physical Exertion, Serotonin, & Glycine (to name a few factors).

It is wise to "sleep in" one-two hours longer the day after an intense workout session to facilitate greater mental and immunological recovery, that is if you have the time and luxury of doing so, but even for the perpetually busy there is always the possibility planning your most difficult and intense workouts for Fridays, or Saturdays, thus allowing you to sleep in, and take frequent naps the day following your exhausting workout.

Dreams

As Sigmund Freud has taught in his work *The Interpretation of Dreams*, dreams are repressed wishes that return during sleep and are fulfilled through the creation of dream stories, composed of direct source material (the wishes) and combined with indifferent visual and audio source material from the previous day(s) and the previous year(s). Dreams are difficult to decipher for three reasons:

1. They are formed with many different new and old memories, memories that are connected together to create metaphorical storylines, new patterns of thought.
2. They are difficult to interpret because they are "censored" and "distorted" by the consciousness, for even during sleep our primary conscious neurons, those that define our behaviors, personality, and morality, are active, but to a lesser extent. A child does not have the capability to censor their dreams, their unconscious, thus they dream of the simplest wishes that require little analysis. Many dreams carry sexual content, which are censored by the dormant but ever active conscious mind.
3. Because most wish fulfillments—most repressed desires, contain negative emotional affectation, during dream formation they are censored, which means they are distorted or disfigured (displaced) by the consciousness in a more subtle form of repression, leading to what many consider the generation of random nonsensical dream content, or more accurately, the generation of confusing metaphorical symbological representations which require careful interpretation.

Wait… "This is nonsense!" You say? Well, let me explain it mechanically;
When we sleep our synapses lose strength through changes in brain wave activity, leading to more neurons, more patterns of neuronal activity becoming activated. Patterns of neuronal activity are responsible for memory formation, memory recollection, behavior formation, and behavior reinforcement, a wish is therefore merely an emotionally tinged potential behavior of forethought that you have had to voluntarily repress, or push from conscious thought, during waking hours. These wishes are dormant but not forgotten, they return during sleep to seek fulfilment, but unlike during waking hours they are now capable of forming into actual hallucinations, which are dreams, because the neurons responsible for our conscious, rational thought, are now dampened—resting, owing to our disconnection from the sensory modalities of reality, and the "censor" is weakened, which may or may not be the total sum of synapses in the brain.

Because adults deal so often in waking life with interpersonal issues with coworkers, family members, and romantic partners, and because the sexual libido is such a strong driving force for most people, dreams are often composed of censored sexual content, and also intrapersonal wishes revolving around the aforementioned people. The monsters that children fear encountering when they are about to fall asleep or encounter during sleep are representations of the unconsciousness, the undeveloped sexual libido, that big and scary force that they do not understand, that lives and hides within their room, and only becomes active during the night. For adults, so too is the fear of sleeping tied to the fear of the sexual

libido and is often related to psycho-sexual moral obstacles i.e. traumatic or repressed sexual memories. It is no coincidence that most sexual acts, most heinous sexual crimes, and the vast majority of criminality occurs in the twilight hours, for this is when the consciousness loses its strength, and the unconsciousness (libido) becomes free, especially during periods of severe drug intoxication.

"For the night terrors with hallucinations (pavor nocturnus) frequently found in children, I would unhesitatingly give the same explanation. Here, too, we are certainly dealing with the incomprehensible and rejected sexual feelings, which, if noted, would probably show a temporal periodicity, for an enhancement of the sexual libido may just as well be produced accidentally through emotional impressions as through the spontaneous and gradual processes of development."
-(d) Waking caused by the Dream—The Function of the Dream—The Anxiety Dream.

Dreams can have a massive impact on emotional wellbeing, whether we remember them or we do not, the fulfilment of our wishes, either in reality or through dream-hallucination protects us from despair and apathy, from social defeat stress, and this is why IQ will always be positively correlated to time spent in the REM stage during sleep, because REM sleep is where the most complex dreams are formed and fulfilled.

It's important to mention that dreams become much harder to decipher when deep sleep is disturbed, or when a human brain is experiencing neurotoxic processes, or when the dreams are not recollected and journaled accurately and quickly upon waking. The act of daydreaming is a sign of mental illness, of synaptic dysfunction, and the prerequisite for the generation of both creativity, and delusional thinking.

"It is in fact the wish-fulfilment that has already induced us to separate dreams into two groups. We have found some dreams that were plainly wish-fulfilments; and others in which wish-fulfilment could not be recognized and was frequently concealed by every available means. In this latter class of dreams we recognized the influence of the dream censor. The undisguised wish dreams were chiefly found in children, yet fleeting open-hearted wish dreams seemed (I purposely emphasize this word) to occur also in adults."
-(c) The Wish-Fulfilment.

"We may now ask whence the wish fulfilled in the dream originates. But to what opposition or to what diversity do we refer this "whence"? I think it is to the opposition between conscious daily life and a psychic activity remaining unconscious which can only make itself noticeable during the night. I thus find a threefold possibility for the origin of a wish. Firstly, it may have been incited during the day, and owing to external circumstances failed to find gratification, there is thus left for the night an acknowledged but unfulfilled wish. Secondly, it may

come to the surface during the day but be rejected, leaving an unfulfilled but suppressed wish."
-(c) The Wish-Fulfilment

"We thus find in the fact that the dream content takes up remnants of trivial experiences a manifestation of dream disfigurement (by means of displacement), and we may recall that we have recognized this dream disfigurement as the work of a censor which controls the passage between two psychic instances. We accordingly expect that dream analysis will regularly reveal to us the genuine, significant source of the dream in the life of the day, the recollection of which has transferred its accent to some indifferent recollection."
-(a) Recent and Indifferent Impressions in the Dream

"The dream is a momentous psychic act; its motive power is at all times to fulfil a wish; its indiscernibleness as a wish and its many peculiarities and absurdities are due to the influence of the psychic censor to which it has been subjected during its formation. Apart from the pressure to withdraw itself from this censor, the following have played a part in its formation: a strong tendency to the condensation of psychic material, a consideration for dramatization into mental pictures, and (though not regularly) a consideration for a rational and intelligible exterior in the dream structure."
-(b) Regression

"Thinking is indeed nothing but the equivalent of the hallucinatory wish; and if the dream be called a wish-fulfilment this becomes self-evident, as nothing but a wish can impel our psychic apparatus to activity. The dream, which in fulfilling its wishes follows the short regressive path, thereby preserves for us only an example of the primary form of the psychic apparatus which has been abandoned as inexpedient. What once ruled in the waking state when the psychic life was still young and unfit seems to have been banished into the sleeping state, just as we see again in the nursery the bow and arrow, the discarded primitive weapons of grown-up humanity. _The dream is a fragment of the abandoned psychic life of the child._ In the psychoses these modes of operation of the psychic apparatus, which are normally suppressed in the waking state, reassert themselves, and then betray their inability to satisfy our wants in the outer world."
↓ continued
"The unconscious wish-feelings evidently strive to assert themselves during the day also, and the fact of transference and the psychoses teach us that they endeavour to penetrate to consciousness and dominate motility by the road leading through the system of the foreconscious. It is, therefore, the censor lying between the Unc. and the Forec., the

assumption of which is forced upon us by the dream, that we have to recognise and honour as the guardian of our psychic health. But is it not carelessness on the part of this guardian to diminish its vigilance during the night and to allow the suppressed emotions of the Unc. to come to expression, thus again making possible the hallucinatory regression? I think not, for when the critical guardian goes to rest—and we have proof that his slumber is not profound—he takes care to close the gate to motility. No matter what feelings from the otherwise inhibited Unc. may roam about on the scene, they need not be interfered with; they remain harmless because they are unable to put in motion the motor apparatus which alone can exert a modifying influence upon the outer world. Sleep guarantees the security of the fortress which is under guard."
-(c) The Wish-Fulfilment.

"Robert therefore conceives the dream "as a physical process of elimination which has reached to cognition in the psychic manifestation of its reaction." Dreams are eliminations of thoughts nipped in the bud. "A man deprived of the capacity for dreaming would surely in time become mentally unbalanced, because an immense number of unfinished and unsolved thoughts and superficial impressions would accumulate in his brain, under the pressure of which there would be crushed all that should be incorporated as a finished whole into memory." The dream acts as a safety-valve for the overburdened brain. Dreams possess healing and unburdening properties."
-(g) Dream Theories and Functions of the Dream.

Dream Analysis

An Example of Dream Analysis 1: The Red Hen

Here is an example of a dream I had that I self-analyzed, it is relatively personal but a perfect description of Freud's collective theories of dream analysis at work:

Previous Days Wishes / Desires: I noticed an attractive woman exercising at my gym, she was fit, and healthy looking, and her skin was glistening with sweat. I was saddened by this because I did not have a girlfriend at the time.

Previous Days Indifferent Memories: I mowed my lawn. I ate cage free eggs for breakfast. I noticed that there was a hen on the carton of eggs that was healthy looking, it had a sheen to its feathers.

Dream Scene 1: I was in my kitchen and noticed a red hen running around my backyard, almost in a sprint. It looked healthy.

Dream Scene 2: I opened the back door and investigated it; it ran into my house to my bed and hid under my covers.

Dream Scene 3: I attempted to make it leave my bed, but it would not.

The censored or distorted character present in this dream was the fit woman I had admired the previous day; she had clearly taken the form of the red hen in this dream.

The two obvious wishes present in this dream, censored and disfigured by my mind:

1. The wild and seemingly untamable woman "entered my home" i.e. she entered into my life, therefore the first wish was to have an attractive, healthy woman become infatuated with me.
2. The red hens entrance into my bed and it's act of hiding under my bed covers and my attempt to make it leave clearly was a socio-sexual representation of the secondary wish; To have the power to rebuke her interest in me out of revenge, to gain power over her, the seemingly unattainable sexual object.

To analyze dreams effectively you will first need to document the scenes of your dreams, each dream scene is a multitude of wish fulfillments, and when one scene ends another will begin, paralleling a change in dream environment or character appearance. Secondly, you should document your previous days' indifferent emotionless memories, such as visual and audio memories. Thirdly, you should document any emotionally charged desires or wishes you had voluntarily repressed during the previous days, weeks, months, or years. You may now begin your analysis, which will involve a high level of metaphorical or analogical representational pattern recognition. The words you use to describe the characters and scenes in your dreams will hold great value for understanding the disfigured, distorted, and censored meanings inherent within them. As evidenced previously, the words "healthy", "bed", and "sprint" held momentous value for properly interpreting my dream, had I not written these words down rapidly upon waking when

remembering my dream my mind may have attempted to censor it further, and it would be nearly impossible to understand.

An Example of Dream Analysis 2: The Mercurial Family

Dream Scene 1: I drove up a long and windy road on a steep hill into a beautiful and luxurious mansion, this mansion was placed on the edge of this steep hill; it overlooked a big lake.

Dream Scene 2: It was a contemporary home with giant glass windows overlooking the lake, I knew it must be worth millions of dollars, the design of the interior, the appliances, all darkly colored, marble and such.

Dream Scene 3: In the middle of the house was a fountain and an art piece that stretched to the high ceiling containing and composed of moving spheres or armillary rings of what appeared to be mercury suspended in floating water, they were coming in and out of small openings in the floor.

Dream Scene 4: I was visiting this house to clean, or perform some menial task, and I noticed in this house there was a woman and a child, and I somehow knew her to be the wife of the wealthy husband who was still at work.

Dream Scene 5: The husband returned home, and some discord occurred between him and his wife, in the argument we all fall into the lake below the house from the glass overlook windows, the husband, the wife, the child, and me.

Dream Scene 6: I am underwater now, and I notice some sort of high technological main system of mercury spheres, this system is sending or transferring the mercury to the house above, I knew them to be toxic, so I evaded them, but the husband did not and died. Strangely, the wife and her child are nowhere to be found, only the husband and I appeared underwater.

In this far more complex dream, I am clearly the wealthy man, the child, and the menial worker, and the mansion atop the steep hill is my contradictory aspirations. The menial worker is a representation of my past self, or my current self, the rather unsuccessful man living on luck, and living day by day, with untapped potential. The menial worker not an active component of the dream, but merely an observer. The mercury art piece which was situated in the middle of the house is a metaphor for the toxic and silent poisons that destroyed the marriage of my parents and may destroy my family in the future, the poisons that come from excessive wealth, luxury, infidelity, prestige, and living a life devoid of God. By witnessing my future self / husband fall from the overlook window and into the lake (my unconscious), and die by being drawn into the mercury reservoir, the wish that was fulfilled was to extinguish the materialistic and uncaring nature of my father, to avoid destroying my future family, my future child, which is an extremely troubling waking thought I have pondered numerous times in my life. There is no doubt there are many other fulfilled wishes in this dream, but the primary wish, the primary

error I was attempting to overcome was regarding a complex intercorrelated and interconnected group of thoughts regarding materialism, marriage, love, wealth, and divorce, simplified as: My wish to avoid becoming my Father.

The Stream of Dreams Hypothesis

Interestingly, scientists up to this point have not adequately researched the correlation between dream formation and Cerebrospinal Fluid (CSF) entrance into the brain during deep sleep. It may be possible that this flow of revitalizing fluid into our brains is intricately tied to dream formation, or at the very least dream facilitation. It is my hypothesis (alongside Robert, and Freud), that if CSF *pulses* in the brain, each CSF *pulse* may stimulate the formation of a dream, or the switch to another dream scene. The hypothetical connection between dream activity and CSF is made stronger by the precise movement pattern of CSF across the brain, where it comes in contact with these brain areas:

- ↓ **(1) Anterior Cingulate Cortex (ACC) (Error detection, Empathy)**
- ↓ **(2) Frontal Lobes (Executive function)**
- ↓ **(3) Basal Forebrain (Acetylcholine release)**
- ↓ **(4) Parietal Lobe (Theory of Mind)**
- ↓ **(5) Temporal Lobe (Fear, Anxiety, Sociality)**
- ↓ **(6) Occipital Lobe (Visual processing)**
- ↓ **(7) Cerebral Cortex (Sensory processing)**

Continuing this hypothesis, if this cascade of brain activity explains some aspect of dream formation then the visual scenes of a dream would be formed long after the dream subject matter—the conceptual or ideational matter—was chosen and refined, and more intriguingly, many dreams would originate from activity in the ACC, which would align with Freud's collaborative theories on dreams, and most especially Wilhelm Roberts impressive work on dream analysis through the prism of natural sciences[1] (who should surely be given most, if not all credit for this mechanical science-based dream formation hypothesis), that is we are to consider repressed wishes & desires as "errors" to our consciousness that are willingly displaced from conscious thought during waking mental life, only to be recollected during sleep. In this hypothetical view dream formation could be considered **Regressive Hallucinatory Error-processing**.

[1] "Robert therefore conceives the dream "as a physical process of elimination which has reached to cognition in the psychic manifestation of its reaction." Dreams are eliminations of thoughts nipped in the bud. "A man deprived of the capacity for dreaming would surely in time become mentally unbalanced, because an immense number of unfinished and unsolved thoughts and superficial impressions would accumulate in his brain, under the pressure of which there would be crushed all that should be incorporated as a finished whole into memory." The dream acts as a safety-valve for the overburdened brain. *Dreams possess healing and unburdening properties*.

-(g) Dream Theories and Functions of the Dream.
-Der Traum Als Naturnothwendigkeit Erklärt by Wilhelm Robert.

Psychological Error-processing, having developed from the most ancient of times in our ancestral evolution has been for so long correlated to survivalism, to species continuation, and this would offer us an explanation as to why human brains must sleep and dream to function effectively, for errors which are not corrected (fulfilled) in waking life, or during sleep, are categorized by the brain as threats to survival, and may begin to overwhelm the system, which explains the steady but predictable progression towards waking hallucination that all people experience when deprived of sleep for long durations of time. The pain or damage (mechanically experienced errors) a less evolved animal experiences when being attacked by a predator or when encountering pain-inducing environmental stimuli is similar to the pain a human being experiences when he or she makes a serious mistake in his socio-sexual life (ERN), physical pain has been steadily replaced by mental pain during our momentous rise from the oceans to the land, and this change from neurological to psychological is one reason for the existence of our impressive and complex consciousness as a species.

If CSF cleanses the brain of molecular trash, and it simultaneously cleanses the mind of unresolved wishes and desires, I must ask:

1. Is this a mechanically explained overlap between matter and mind?

2. What role do beta-amyloid, tau, and a-synuclein play in dream formation, are they faciliatory or inhibitory to the process? Considering these proteins play a positive role in neuronal maintenance if their concentrations are controlled, it can be assumed one or more of these proteins are faciliatory to the process of dream formation.

3. If chronic unpredictable stress and loneliness are eventually proven beyond a reasonable doubt to promote amyloid deposition or the progression towards any form of dementia, is this to be considered a novel defense mechanism the brain takes to prevent the reactivation of memories, of errors encountered in waking life, ones that cause the recurrence of psychological stress?

3.1. Could neurodegeneration resulting from psychological stress be a way for the brain to decrease the generation of social defeat stress due to reduced cognitive function, for is ignorance not bliss until it becomes pathological?

The Four Primary Stages of Sleep

Stage-1: Non-Rapid Eye Movement (NREM) Sleep: Relaxed muscle tone, decreased heart rate.

Stage-2: Non-Rapid Eye Movement (NREM) Sleep: Increased relaxation of muscle tone, further decrease in heart rate.

Stage-3: Slow Wave (SWS) Sleep: Entrance into restorative “deep sleep”, enhanced immunological activity (wound healing), early memory consolidation begins that involves simplistic information such as names, dates, & stories.

Stage-4: Rapid Eye Movement (REM) Sleep: Entrance into the dreamworld (unconsciousness: dormant neurons become active), paralysis of muscles occurs, maximized memory consolidation begins that involves complex ideas, concepts, and emotions, thus resulting in the promotion of maximized behavioral flexibility and psychological conditioning / reconditioning.

Sleep Spindles are brain wave activity patterns that occur during sleep, they promote the transfer of information necessary for long term memory consolidation, they originate from the Thalamus and spread to the cortex. The existence of these precise brain wave patterns provides merit to my hypothesis on the existence of Hypercomplex Action Potential Signatures (information) stored within each individual neuron.

Napping

Naps do not promote permanent memory consolidation by way of SWS or REM sleep, instead they likely promote memory retrieval and recollection through enhancing synaptic efficiency, through *Process O*, which is a new biological process that has been hypothesized by Nicole Lovato, & Leon Lack, of which explains that post-nap memory improvements are a direct result of the rapid reactivation (rebooting) of *wake-active cells following the aforementioned nap, thereby resulting in improved memory performance:

*Cells that are active during the day and facilitate consciousness, as opposed to cells that are active during sleep and facilitate unconsciousness (dream formation).

"<>Naps (brief sleeps) are a global and highly prevalent phenomenon, thus warranting consideration for their effects on cognitive functioning. Naps can reduce sleepiness and improve cognitive performance. The benefits of brief (5-15 min) naps are almost immediate after the nap and last a limited period (1-3h). Longer naps (> 30 min) can produce impairment from sleep inertia for a short period after waking but then produce improved cognitive performance for a longer period (up to many hours). Other factors that affect the benefits from the nap are the circadian timing of the nap with early afternoon being the most favourable time. Longer periods of prior wakefulness favour longer naps over brief naps. Those who regularly nap seem to show greater benefits than those who rarely nap.
<>These conclusions, however, need to be accepted cautiously until more comprehensive research programmes are conducted in which all these parameters are varied. Research is also needed to test the benefits of brief naps taken more naturalistically at the time when sleepiness becomes intrusive. The significant benefits of a brief nap, containing virtually no slow wave EEG activity, are not predicted by the present theory of homeostatic sleep drive (Process S).
<>A new biological process (Process O) suggests that sleep onset followed by only 7-10 min of sleep can result in a substantial increase of alertness because it allows the rapid dissipation of inhibition in the 'wake-active' cells associated with the 'sleep-switch' mechanism rather than the dissipation of Process S."[85.4.6]

Adenosine Receptors A1 / A2A are similar to GABA receptors in that they are inhibitory to brain electrical activity, but they are predominately associated with the promotion of slow-wave sleep, and bDNF-related synaptic plasticity. They reduce cholinergic activity in the brain to facilitate REM sleep. Sleep deprivation increases the concentration of Adenosine-1 Receptor binding in the brain, thereby promoting the feeling of "sleepiness".

[A] A2A receptors promote all forms of sleep, especially REM sleep.

"<>We examined the sleep-modulatory effects of four adenosine agonists, namely, (1) 2-(4-(2-carboxyethyl)phenylethylamino)adenosine-5'-N-ethylcarbo xamideadenosine (CGS21680), a highly selective adenosine A2A receptor agonist; (2) 2-(4-(2-(2-aminoethylaminocarbonyl)ethyl)phenylethylamino)-5 '-N-ethylcarboxamidoadenosine (APEC), a selective adenosine A2A receptor agonist; (3) 5'-N-ethylcarboxamidoadenosine (NECA), a nonselective adenosine A1/A2 receptor agonist, and (4) N6-cyclopentyladenosine (CPA), a selective adenosine A1 receptor agonist.
<>Each agonist was administered in the subarachnoid space underlying the rostral basal forebrain of rats through chronically implanted cannulae at the rate of 0.02, 0.2, 2.0, 12.0, or 20.0 pmol/min over a 6-h period starting from 2300 h, which period is the active phase of the animals.
<>CGS21680, APEC, and NECA produced significant increases in the total amounts of non-rapid-eye-movement (NREM) sleep and rapid-eye-movement (REM) sleep after at least one dose within the range of administration rates. CPA did not produce any significant increase in the total amount of either type of sleep at any of the above administration rates, but instead suppressed REM sleep at the administration rates of 12.0 and 20.0 pmol/min.
<>These results indicate that the activities of adenosine A2A receptors are crucially involved in the promotion of sleep."[85.4.7]

[A2] Adenosine A1 Receptor binding is increased after sleep deprivation.

"<>It is currently hypothesized that adenosine is involved in the induction of sleep after prolonged wakefulness. This effect is partially reversed by the application of caffeine, which is a nonselective blocker of adenosine receptors. Here, we report that the most abundant and highly concentrated A1 subtype of cerebral adenosine receptors is upregulated after 24 h of sleep deprivation. We used the highly selective A1 adenosine receptor (A1AR) radioligand [18F]CPFPX ([18F]8-cyclopentyl-3-(3-fluoropropyl)-1-propylxanthine) and quantitative positron emission tomography to assess cerebral A1ARs before and after sleep deprivation in 12 healthy volunteers and a control group (n = 10) with regular sleep.
<>In sleep deprived subjects, we found an increase of the apparent equilibrium total distribution volume in a region-specific pattern in all examined brain regions with a maximum increase in the orbitofrontal cortex (15.3%; p = 0.014). There were no changes in the control group with regular sleep. This is the first molecular imaging study that provides in vivo evidence for an A1AR upregulation in cortical and subcortical brain regions after prolonged wakefulness, indicating that A1AR expression is contributing to the homeostatic sleep regulation."[85.5]

[A3] Extended sleep deprivation causes "long lasting" reductions in Adenosine A2A receptor binding.

"<>Although chronic sleep restriction frequently produces long-lasting behavioural and physiological impairments in humans, the underlying neural mechanisms are unknown.

Here we used a rat model of chronic sleep restriction to investigate the role of brain adenosine and noradrenaline systems, known to regulate sleep and wakefulness, respectively. The density of adenosine A1 and A2a receptors and β-adrenergic receptors before, during and following 5 days of sleep restriction was assessed with autoradiography. Rats (n = 48) were sleep-deprived for 18 h day–1 for 5 consecutive days (SR1–SR5), followed by 3 unrestricted recovery sleep days (R1–R3). Brains were collected at the beginning of the light period, which was immediately after the end of sleep deprivation on sleep restriction days.
<>Chronic sleep restriction increased adenosine A1 receptor density significantly in nine of the 13 brain areas analysed with elevations also observed on R3 (+18 to +32%). In contrast, chronic sleep restriction reduced adenosine A2a receptor density significantly in one of the three brain areas analysed (olfactory tubercle which declined 26–31% from SR1 to R1). A decrease in b-adrenergic receptors density was seen in substantia innominata and ventral pallidum which remained reduced on R3, but no changes were found in the anterior cingulate cortex. These data suggest that chronic sleep restriction can induce long-term changes in the brain adenosine and noradrenaline receptors, which may underlie the long-lasting neurocognitive impairments observed in chronic sleep restriction."[85.6]

[A4] Adenosine A2Ar's are necessary for bDNF transmission and its memory promoting actions in the brain.

"<>Brain-derived neurotrophic factor (BDNF), a member of neurotrophin family, enhances synaptic transmission and regulates neuronal proliferation and survival. Both BDNF and its tyrosine kinase receptors (TrkB) are highly expressed in the hippocampus, where an interaction with adenosine A(2A) receptors (A(2A)Rs) has been recently reported. In the present paper, we evaluated the role of A(2A)Rs in mediating functional effects of BDNF in hippocampus using A(2A)R knock-out (KO) mice. In hippocampal slices from WT mice, application of BDNF (10 ng/mL) increased the slope of excitatory post-synaptic field potentials (fEPSPs), an index of synaptic facilitation. This increase of fEPSP slope was abolished by the selective A(2A) antagonist ZM 241385. Similarly, genetic deletion of the A(2A)Rs abolished BDNF-induced increase of the fEPSP slope in slices from A(2A)R KO mice The reduced functional ability of BDNF in A(2A)R KO mice was correlated with the reduction in hippocampal BDNF levels.
<>In agreement, the pharmacological blockade of A(2)Rs by systemic ZM 241385 significantly reduced BDNF levels in the hippocampus of normal mice. These results indicate that the tonic activation of A(2A)Rs is required for BDNF-induced potentiation of synaptic transmission and for sustaining a normal BDNF tone in the hippocampus."[85.7]

[A5] Unfortunately, while Adenosine A1 / A2A receptors appear to promote sleep & bDNF expression, they are liable to exacerbate cognitive decline during aging, making caffeine a necessary nootropic for the aging human brain (at the cost of blood vessel number).

"<>Immunostaining of adenosine receptors in the hippocampus and cerebral cortex from necropsies of Alzheimer disease (AD) patients shows that there is a change in the pattern of expression and a redistribution of receptors in these brain areas when compared with samples from controls. Adenosine A1 receptor (A1R) immunoreactivity was found in degenerating neurons with neurofibrillary tangles and in dystrophic neurites of senile plaques. A high degree of colocalization for A1R and betaA4 amyloid in senile plaques and for A1R and tau in neurons with tau deposition, but without tangles, was seen. Additionally, adenosine A2A receptors, located mainly in striatal neurons in controls, appeared in glial cells in the hippocampus and cerebral cortex of patients.
<>On comparing similar samples from controls and patients, no significant change was evident for metabotropic glutamate receptors. In the human neuroblastoma SH-SY5Y cell line, agonists for A1R led to a dose-dependent increase in the production of soluble forms of amyloid precursor protein in a process mediated by PKC. A1R agonist induced p21 Ras activation and ERK1/2 phosphorylation. Furthermore, activation of A1R led to and ERK-dependent increase of tau phosphorylation and translocation towards the cytoskeleton. These results indicate that adenosine receptors are potential targets for AD."[85.8]

[B] Sleep deprivation reduces protein synthesis and testosterone; it is therefore not advisable to reduce sleep quality for a natural athlete.

"<>Chronic sleep loss is a potent catabolic stressor, increasing the risk of metabolic dysfunction and loss of muscle mass and function. To provide mechanistic insight into these clinical outcomes, we sought to determine if acute sleep deprivation blunts skeletal muscle protein synthesis and promotes a catabolic environment. Healthy young adults (N = 13; seven male, six female) were subjected to one night of total sleep deprivation (DEP) and normal sleep (CON) in a randomized cross-over design. Anabolic and catabolic hormonal profiles were assessed across the following day. Postprandial muscle protein fractional synthesis rate (FSR) was assessed between 13:00 and 15:00 and gene markers of muscle protein degradation were assessed at 13:00. Acute sleep deprivation reduced muscle protein synthesis by 18% (CON: 0.072 ± 0.015% vs. DEP: 0.059 ± 0.014%·h-1 , p = .040).
<>In addition, sleep deprivation increased plasma cortisol by 21% (p = .030) and decreased plasma testosterone by 24% (p = .029). No difference was found in the markers of protein degradation. A single night of total sleep deprivation is sufficient to induce anabolic resistance and a procatabolic environment. These acute changes may represent mechanistic precursors driving the metabolic dysfunction and body composition changes associated with chronic sleep deprivation."[86.0]

[C] Sleep deprivation reduces mTOR activity in the brain.

"<>Sleep deprivation is a public health epidemic that causes wide-ranging deleterious consequences, including impaired memory and cognition. Protein synthesis in hippocampal neurons promotes memory and cognition. The kinase complex mammalian

target of rapamycin complex 1 (mTORC1) stimulates protein synthesis by phosphorylating and inhibiting the eukaryotic translation initiation factor 4E binding protein 2 (4EBP2). We investigated the involvement of the mTORC1-4EBP2 axis in the molecular mechanisms mediating the cognitive deficits caused by sleep deprivation in mice. Using an in vivo protein translation assay, we found that loss of sleep impaired protein synthesis in the hippocampus.
<>Five hours of sleep loss attenuated both mTORC1-mediated phosphorylation of 4EBP2 and the interaction between eukaryotic initiation factor 4E (eIF4E) and eukaryotic initiation factor 4G (eIF4G) in the hippocampi of sleep-deprived mice. Increasing the abundance of 4EBP2 in hippocampal excitatory neurons prior to sleep deprivation increased the abundance of phosphorylated 4EBP2, restored the amount of eIF4E-eIF4G interaction and hippocampal protein synthesis to that seen in mice that were not sleep-deprived, and prevented the hippocampus-dependent memory deficits associated with sleep loss.
<>These findings collectively demonstrate that 4EBP2-regulated protein synthesis is a critical mediator of the memory deficits caused by sleep deprivation."[86]

[D] One night of sleep deprivation enhances neurogenesis.

"<>Neurogenesis in the adult hippocampus can be up- or downregulated in response to a variety of physiological and pathological conditions. Among these, dysregulation of hippocampal neurogenesis has been recently implicated in the pathogenesis of depression. In addition, in animal models of depression, a variety of antidepressant treatments reverse that condition by increasing neurogenesis. As one night sleep deprivation is known to improve mood in depressed patients for at least 1 day, we investigated whether a comparable treatment may affect hippocampal neurogenesis in adult rats. Accordingly, rats were sleep-deprived by gentle handling for 12 h during their physiological period of rest, and were injected with bromodeoxyuridine 4 h and 2 h before the end of sleep deprivation. They were then perfused immediately thereafter, or after 15 days and 30 days.
<>We found that 12 h sleep deprivation significantly increased cell proliferation and the total number of surviving cells in the hippocampal dentate gyrus soon after sleep deprivation, as well as 15 days and 30 days later, in comparison to control rats allowed to sleep. No changes were instead found in the subventricular zone of the lateral ventricles, indicating that 12 h sleep deprivation selectively triggers neurogenic signals to the hippocampus. The present data include acute sleep deprivation among the conditions which upregulate hippocampal neurogenesis and raise the possibility that such response could be implicated in the beneficial effects elicited in depressed patients by one night sleep deprivation. Thus, the findings could contribute to the understanding of the intriguing relationship between depression and neurogenesis in the adult brain."[87]

[E] Short term Sleep deprivation does not impact wound healing.

“Sleep deprivation is widely regarded as a stressor and has been shown to have significant effects on host defenses. Severely sleep-deprived rats develop lesions on their paws and tails, suggesting possible deficits in the healing process. The purpose of this study was to assess the impact of rapid eye-movement (REM) sleep deprivation (RSD) on wound healing in a rat model. Male dark-hooded Long-Evans rats, 2-4 months old, were subjected to dorsal application of two sterile punch biopsies, each 3.5 mm in size. Biopsies were performed either immediately before or immediately after 5 days of sleep deprivation. Wound healing in REM sleep-deprived animals was compared with home cage control and yoked control animals. RSD did not produce differences in the rate of healing, regardless of the timing of the biopsy punch. RSD does not appear to have significant effects on wound healing and thus appears to act differently from other types of stressors on wound healing.”[88]

[F] Rapid Eye Movement Sleep is essential for memory consolidation 1.

“<>Study objectives: Memory reactivation appears to be a fundamental process in memory consolidation. In this study we tested the influence of memory reactivation during rapid eye movement (REM) sleep on memory performance and brain responses at retrieval in healthy human participants.
<>Participants: Fifty-six healthy subjects (28 women and 28 men, age [mean ± standard deviation]: 21.6 ± 2.2 y) participated in this functional magnetic resonance imaging (fMRI) study.
<>Methods and results: Auditory cues were associated with pictures of faces during their encoding. These memory cues delivered during REM sleep enhanced subsequent accurate recollections but also false recognitions. These results suggest that reactivated memories interacted with semantically related representations, and induced new creative associations, which subsequently reduced the distinction between new and previously encoded exemplars. Cues had no effect if presented during stage 2 sleep, or if they were not associated with faces during encoding. Functional magnetic resonance imaging revealed that following exposure to conditioned cues during REM sleep, responses to faces during retrieval were enhanced both in a visual area and in a cortical region of multisensory (auditory-visual) convergence.
<>Conclusions: These results show that reactivating memories during REM sleep enhances cortical responses during retrieval, suggesting the integration of recent memories within cortical circuits, favoring the generalization and schematization of the information.”[89]

[F2] Rapid Eye Movement Sleep is essential for memory consolidation 2.

“<>Study objectives: Prospective memory, or remembering to execute future intentions, accounts for half of everyday forgetting in older adults. Sleep intervals benefit prospective memory consolidation in young adults, but it is unknown whether age-related changes in slow wave activity, sleep spindles, and/or rapid eye movement (REM) sleep mediate hypothesized effects of aging on prospective memory consolidation.

<>Methods: After an adaptation night, 76 adults aged 18-84 completed two experimental nights of in-laboratory polysomnography recording. In the evening, participants encoded and practiced a prospective memory task and were tested the next morning. On a counterbalanced night, they encoded and practiced a control task, and were tested the following morning.
<>Results: Increasing age predicted worse prospective memory consolidation (r = -.34), even when controlling for encoding, speed, and control-task performance (all ps < .05). Frontal delta power, slow oscillations, and spindle density were not related to prospective memory consolidation. REM sleep duration, however, explained significant variance in prospective memory consolidation when controlling for age (ΔR2 = .10). Bootstrapping mediation showed that less REM sleep significantly mediated the aging effect on prospective memory consolidation [b = -.0016, SE = 0.0009 (95% confidence interval [CI] = -0.0042 to -0.0004)]. REM sleep continued to mediate 24.29% of the total effect of age on prospective memory after controlling for numerous demographic, cognitive, mental health, and sleep variables.
<>Conclusion: Age-related variance in REM sleep is informative to how prospective memory consolidation changes with increasing age. Future work should consider how both REM sleep and slow wave activity contribute, perhaps in a sequential or dynamic manner, to preserving cognitive functioning with increasing age."[90]

[G] Low brain levels of Acetylcholine are important for motor memory consolidation during sleep. This means that if you're learning a new exercise and you consume copious amounts of chemicals with long half-lives that increase brain acetylcholine levels you will not retain (to the maximal degree) the motor memories learned.

"<>The synaptic homeostasis theory of sleep proposes that low neurotransmitter activity in sleep optimizes memory consolidation. We tested this theory by asking whether increasing acetylcholine levels during early sleep would weaken motor memory consolidation. We trained separate groups of adult mice on the rotarod walking task and the single pellet reaching task, and after training, administered physostigmine, an acetylcholinesterase inhibitor, to increase cholinergic tone in subsequent sleep. Post-sleep testing showed that physostigmine impaired motor skill acquisition of both tasks. Home-cage video monitoring and electrophysiology revealed that physostigmine disrupted sleep structure, delayed non-rapid-eye-movement sleep onset, and reduced slow-wave power in the hippocampus and cortex.
<>Additional experiments showed that: (1) the impaired performance associated with physostigmine was not due to its effects on sleep structure, as 1 h of sleep deprivation after training did not impair rotarod performance, (2) a reduction in cholinergic tone by inactivation of cholinergic neurons during early sleep did not affect rotarod performance, and (3) stimulating or blocking muscarinic and nicotinic acetylcholine receptors did not impair rotarod performance. Taken together, the experiments suggest that the increased slow wave activity and inactivation of both muscarinic and nicotinic receptors during early sleep due to reduced acetylcholine contribute to motor memory consolidation."[91]

[H] Glycine activates the suprachiasmatic nucleus (circadian rhythm nuclei) to promote sleep.

"<>The use of glycine as a therapeutic option for improving sleep quality is a novel and safe approach. However, despite clinical evidence of its efficacy, the details of its mechanism remain poorly understood. In this study, we investigated the site of action and sleep-promoting mechanisms of glycine in rats. In acute sleep disturbance, oral administration of glycine-induced non-rapid eye movement (REM) sleep and shortened NREM sleep latency with a simultaneous decrease in core temperature. <>Oral and intracerebroventricular injection of glycine elevated cutaneous blood flow (CBF) at the plantar surface in a dose-dependent manner, resulting in heat loss. Pretreatment with N-methyl-D-aspartate (NMDA) receptor antagonists AP5 and CGP78608 but not the glycine receptor antagonist strychnine inhibited the CBF increase caused by glycine injection into the brain. Induction of c-Fos expression was observed in the hypothalamic nuclei, including the medial preoptic area (MPO) and the suprachiasmatic nucleus (SCN) shell after glycine administration. Bilateral microinjection of glycine into the SCN elevated CBF in a dose-dependent manner, whereas no effect was observed when glycine was injected into the MPO and dorsal subparaventricular zone. In addition, microinjection of D-serine into the SCN also increased CBF, whereas these effects were blocked in the presence of L-701324. SCN ablation completely abolished the sleep-promoting and hypothermic effects of glycine.
<>These data suggest that exogenous glycine promotes sleep via peripheral vasodilatation through the activation of NMDA receptors in the SCN shell."[92]

[I] GABAA Receptor agonism enhances NREM sleep but reduces SWS / REM sleep, thus reducing the intelligence (memory consolidation) of those who unknowingly use insomnia medications and sleep-promoting supplements that act through the GABAA receptors. There are many studies that will say the opposite, but these are likely to be funded by certain pharmaceutical companies.
It makes perfect mechanical sense that a chemical that is inhibitory, and reduces glutamate in the brain, would interrupt the progression to deeper stages of sleep, which are dependent on NMDA receptor activity (excitement). Memories are only stored in the brain through excitation, even during sleep.

"<>This paper reviews the sleep effects of systemically administered agonistic modulators of GABAA receptors, including barbiturates, benzodiazepines, zolpidem, zopiclone and neuroactive steroids, and the selective GABAA agonists muscimol and THIP. To assess the involvement of GABAA receptors in the physiologic regulation of sleep, the article emphasizes the hypnotic properties shared by agonistic modulators and by the selective agonists of the GABAA receptor complex.
<>In both rats and normal sleeping individuals, agonistic modulators are able to reduce sleep latency, increase sleep continuity, and promote non-rapid-eye-movement (NREM) sleep as well as the occurrence of spindles. Furthermore, nearly all of these compounds have been shown to attenuate slow-wave activity (SWA) and to suppress the occurrence

of REM sleep. In the same species, GABAA agonist(s) do not seem to affect sleep latency or REM sleep time but may increase sleep continuity and NREM sleep and augment SWA while depressing spindle activity in humans.
<>The distinct sleep effects of GABAA agonists may be due to their unspecific stimulation of GABAA receptors throughout the brain, and to the fact that they are poor substrates for uptake and probably exert more tonic effects than liberated GABA. If so, the involvement of GABAA receptors in the various aspects of sleep can be inferred more accurately from the hypnotic effects of agonistic modulators. <>This implies that an activation of GABAA receptors plays a crucial role in the initiation and maintenance of NREM sleep and in the generation of sleep spindles but disrupts the processes underlying slow EEG components and the triggering of REM sleep."[92.1]

[J] Nerve Growth Factor enhances Rapid Eye Movement Sleep! The future of sleep supplements has been found. [See: Anti-Inflammation Cycle Supplementation: Lion's Mane Mushroom]

"Nerve growth factor (NGF) elicits rapid-eye-movement sleep (REMS) in cats. Removal of NGF receptor-positive cholinergic basal forebrain neurons inhibits REMS in rats. The aim of the present study was to determine the effects of NGF on sleep and brain temperature (Tbr) in rabbits. Male rabbits were implanted with electroencephalograph (EEG) electrodes, a brain thermistor and an intraventricular (i.c.v.) guide cannula. Rabbits received human beta-NGF i.c.v. (0.01, 0.1, 1.0 or 10 microg] and on a separate day, 25 microl pyrogen-free saline i.c.v. as control. EEG and Tbr were recorded for 23 h after injections. The highest two doses of NGF increased both non-REMS and REMS across the 23-h recording period. REMS was enhanced dose-dependently. Tbr was not affected by any dose of NGF. These results suggest that NGF is involved in both REMS and non-REMS regulation."[93]
[K] Sleep Deprivation reduces AMPA Receptor activity, thereby impairing memory.

"<>Sleep is important for brain function and cognitive performance. Sleep deprivation (SD) may affect subsequent learning capacity and ability to form new memories, particularly in the case of hippocampus-dependent tasks. In the present study we examined whether SD for 6 or 12 h during the normal resting phase prior to learning affects hippocampus-dependent working memory in mice. In addition, we determined effects of SD on hippocampal glutamate alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors and their regulatory pathways, which are crucially involved in working memory.
<>After 12 h SD, but not yet after 6 h, spatial working memory in a novel arm recognition task was significantly impaired. This deficit was not likely due to stress as corticosterone levels after SD were not significantly different between groups. In parallel with the change in cognitive function, we found that 12 h SD significantly reduced hippocampal AMPA receptor phosphorylation at the GluR1-S845 site, which is important for incorporation of the receptors into the membrane. SD did not affect protein levels of cyclic-AMP-dependent protein kinase A (PKA) or phosphatase calcineurin (CaN), which

regulate GluR1 phosphorylation. However, SD did reduce the expression of the scaffolding molecule A-kinase anchoring protein 150 (AKAP150), which binds and partly controls the actions of PKA and CaN.
<>In conclusion, a relatively short SD during the normal resting phase may affect spatial working memory in mice by reducing hippocampal AMPA receptor function through a change in AKAP150 levels. Together, these findings provide further insight into the possible mechanism of SD-induced hippocampal dysfunction and memory impairment."[93.0]

[L] 30-Minute Naps appear to be perfect for enhancing memory.

"<>Study Objectives: To determine how mid-afternoon naps of differing durations benefit memory encoding, vigilance, speed of processing (SOP), mood, and sleepiness; to evaluate if these benefits extend past 3 hr post-awakening and to examine how sleep macrostructure during naps modulate these benefits.
<>Methods: Following short habitual sleep, 32 young adults underwent four experimental conditions in randomized order: wake; naps of 10 min, 30 min, and 60 min duration verified with polysomnography. A 10-min test battery was delivered at a pre-nap baseline, and at 5 min, 30 min, 60 min, and 240 min post-nap. Participants encoded pictures 90 min post-nap and were tested for recognition 210 min later.
<>Results: Naps ranging from 10 to 60 min increased positive mood and alleviated self-reported sleepiness up to 240 min post-nap. Compared to waking, only naps of 30 min improved memory encoding. Improvements in vigilance were moderate, and benefits for SOP were not observed. Sleep inertia was observed for the 30 min to 60 min naps but was resolved within 30 min after waking. We found no significant associations between sleep macrostructure and memory benefits.
<>Conclusions: With short habitual sleep, naps ranging from 10 to 60 min had clear and lasting benefits for positive mood and self-reported sleepiness/alertness. Cognitive improvements were moderate, with only the 30 min nap showing benefits for memory encoding. While there is no clear "winning" nap duration, a 30 min nap appears to have the best trade-off between practicability and benefit."
"All nap durations improved alertness and increased positive mood. However, compared to wake, a 30 min nap incurred minimal sleep inertia and benefitted memory encoding. With 10–15 min of sleep latency in mind, one should apportion ~40–45 min to obtain 30 min of sleep for a midday refresh for learning and mood improvement."[93.A]

[M] Shift-work (work schedules that interfere with a normal circadian rhythm), cause the suppression of a growth factor in the body called Early Growth Response 3, which suppresses adipogenesis through Histone Deacetylase-6 activity. This occurs likely through enhanced Cortisol secretion, to thereby promote adipogenesis, highlighting the vital need of cortisol inhibitor use in night workers.
"<>The disruption of circadian rhythms caused by long-term shift work can cause metabolic diseases such as obesity. Early growth response 3 (EGR3) is a member of early growth response (EGR) family, which is involved in several cellular responses, had been

reported as a circadian rhythm gene in suprachiasmatic nucleus. In this research, EGR3 was found to be widely expressed in the different tissue of human and mice, and downregulated in adipose tissue of obese subjects and high-fat diet mice. Moreover, EGR3 was found negatively regulated by cortisol. In addition, EGR3 is a key negative modulator of hADSCs and 3T3-L1 adipogenesis via regulating HDAC6, which is a downstream target gene of EGR3 and a negative regulator of adipogenesis and lipogenesis. These findings may explain how circadian rhythm disorder induced by shift works can cause obesity. Our study revealed a potential therapeutic target to alleviate metabolic disorders in shift workers and may

provide better health guidance to shift workers."[93.A1]

Circadian Entrainment

This biological process describes the synchronization of the 24h day-night cycle, it involves light entering through the eyes forming specific signals in the brain which reach the Suprachiasmatic Nucleus (SCN) to the biological sleep-wake cycle of hormone secretion, metabolism, and body temperature. We can engage in Circadian Entrainment to promote physical and mental health in three simple ways, firstly is to utilize the sun's electromagnetic radiation to promote wakefulness by allowing sunlight to enter through our eyelids, this is often accomplished unintentionally during normal wake cycles but can be further magnified through closed eye sunbathing, where one allows sunlight to radiate through their eyelids for a few minutes upon waking, the second way is to restrict the use of technology that emits blue light, as this wavelength signals the SCN to promote the expression of wake-promoting genes, and neurotransmitters such as dopamine, and the third way is to use Melatonin, a "Chronobiotic", which signals the SCN to activate the sleep cycle.

Interestingly, the activation of the SCN sleep cycle through Chronobiotic use, even in the absence of sleep, is likely to promote homeostatic, neuroprotective, and antioxidant mechanisms due to the activation of genes that increase during sleep, such as bDNF and SIRT1, thus potentially explaining the neuroprotective and nootropic effects of Melatonin use and highlighting its potential use even during hours of wake.

"<>Both the clock mechanism and the entrainment pathway represent extremely robust processes that have been fairly conserved in evolutionary terms. Photic input to the clock seems to have been spared from the need of cognitive vision, since there are several indications of entrainment in the absence of conscious visual cues. The dynamics of the SCN appear to be well adapted to both the daily photoperiod and its seasonal variation. A well-adapted temporal niche is certainly relevant for survival, and photic and nonphotic cues contribute to a correct temporal allocation of resources and physiological economies.

<>However, we could consider human circadian rhythms in the post-Edison era as an aberration in terms of adaptation to their natural environment. It has been said that we are prepared for a world that does not exist anymore, with reliable external markers for

timing that are not masked by artificial cues. Life in this “Enlightment” era comes accompanied by specific circadian disruptions that could be considered a sign of our times. Among these, adaptation to rotating or abruptly changed time schedules (such as shift work or jetlag) is limited by the inertia of the circadian system that, although plastic, exhibits difficulties in adjusting to changing environments. Indeed, chronic circadian disruptions (which are considered a particular sleep disord) lead not only to an impairment in the sleep-wake cycle, but also to reduced performance and productivity, a higher accident rate, and even serious health risks.
<>Treatment for circadian sleep disruptions include chronotherapy (i.e., behavioral phase shifting of rhythms until the right phase is achieved), phototherapy (light treatment), and the pharmacological use of chronobiotics, i.e., compounds that move the hands of the circadian clock. Indeed, two of the most studied agents for changing the speed and phase of circadian oscillations are light and the pineal hormone melatonin. Although important phase shifting capabilities have been found for melatonin and a variety of compounds in human circadian rhythms, it is clear that the main entrainment agent in most terrestrial animals is light.
<>When appropriately administered and timed, photic stimulation is able to phase shift human circadian rhythms, including the sleep-wake cycle, and accommodate the circadian phase to the desired time point. Light is cheap (and even free, when considering a nice diurnal walk in the park as a potential therapeutic agent), very effective and, when properly used, without any side effects, so combining any circadian treatment with some kind of photic therapy is certainly bound for success. Circadian and sleep clinical trials are sometimes heroic efforts, with relatively low levels of compliance; however, the figures available for people suffering some form of circadian-related transient insomnia (including an estimated 20% of the work force undergoing some kind of shift work schedule and an unknown prevalence of jetlag-related disorders) deserve the best of our efforts.”[93.A2]

Chrononutrition

The composition of macronutrients consumed throughout the day, especially before going to sleep, have a pronounced effect on sleep hygiene. The less glycine and the less carbohydrates you consume before bed will nearly always result in a decrease in sleep efficiency, due two primary reasons, the first being a lack of signaling to the Suprachiasmatic Nucleus, the second being the potential occurrence of hypoglycemia, resulting in the promotion of a stress response. For those who find it terribly difficult to reset their circadian rhythm to normalcy, it is necessary in my opinion to first reset their way of eating to a more primitive mode. This entails time-restricted eating; eating one large high protein, moderate carbohydrate, moderate fat meal in the evening before going to sleep. Doing so should effectively synchronize the circadian rhythm to the natural wake-sleep cycle of daylight hours to nighttime hours by stimulating a surplus of cortisol during the fasted waking hours thereby signaling to the brain that you are in the wake cycle, and by stimulating neurotransmitter release in the evening hours through a macronutrient-rich meal, signaling to the brain that it is nearly time to rest.

Progressive Sleep Scheduling

Most of us understand that by the end of a workweek we are tired, we are physically sore, and we require the weekend to recover, through both detraining and through "sleeping in". To form a sleep schedule that aligns to the exigencies of work, exercise, and accumulating fatigue, I posit that a sleep schedule should be defined by either a progressive or intermittent algorithm. See the example below for the progressive variation:

M: 6:00AM Wake: AM Very Low Intensity Exercise (or Quinary Targeted Muscles).
T: 7:00AM Wake: AM Low Intensity Exercise (or Quaternary Targeted Muscles).
W: 8:00AM Wake: PM Moderate Intensity Exercise (or Tertiary Targeted Muscles).
T: 9:00AM Wake: PM High Intensity Exercise (or Secondary Targeted Muscles).
F: 10:00AM Wake: PM Max Intensity Exercise (or Primary Targeted Muscles).
S-S: Sleep in.

We see in this example sleep schedule that the sleep permitted each night steadily progressives to a peak wherein the weekend comes, and sleep is completely undisturbed. By allowing your body greater recovery time each day, dependent on exercise intensity, or targeted muscles (muscles that you wish to provide the greatest chance for growth through sleep recovery). Assuming that your work schedule is static, you should set your Monday waking hour to between five-six hours before work, so you can train immediately upon waking on Monday-Tuesday, but on Wednesday-Thursday-Friday you will train after work in the evening, leading to a greater anabolic biological milieu being available for your targeted muscles to grow within, because evening exercise will always be more anabolic than morning exercise, due to the decreased release of stress hormones, greater amino acid availability pre-workout, and potentially the facilitation of a myogenic circadian rhythm, which naturally increases protein synthesis later in the day.

Intermittent Sleep Scheduling

This is another sleep schedule to allot more time for exercising, and is best paired with morning training and endurance protocols. By waking up early once or twice a week, you gain the opportunity to eat more, ensure that there is adequate free time for your warmups and post-exercise myogenic modalities, and for endurance exercise you will be able to squeeze hours' long workouts into your busy days. See the examples below:

(SSCD)
M: 6:00AM Wake: AM Upper-Body Max Volume Endurance.
T/W: 8:00AM Wake: AM Lower-Body Low Volume Endurance.
T: 6:00AM Wake: AM Lower-Body Max Volume Endurance.
F: 8:00AM Wake: AM Lower-Body Low Volume Endurance.

S-S: Sleep in.
(Simple ARCS Program)
M: 6:00AM Wake: AM Press/Row Occlusion + Modalities.
T: 8:00AM Wake: AM Short Duration Lower-Body SS-Cardio.
W: 6:00AM Wake: AM Press/Row Warmups + Modalities.
T: 8:00AM Wake: AM Short Duration Lower-Body SS-Cardio.
F: 6:00AM Wake: AM Press/Row Strength + Modalities.
S-S: Sleep in.

Brain Waves & Error-related Negativity

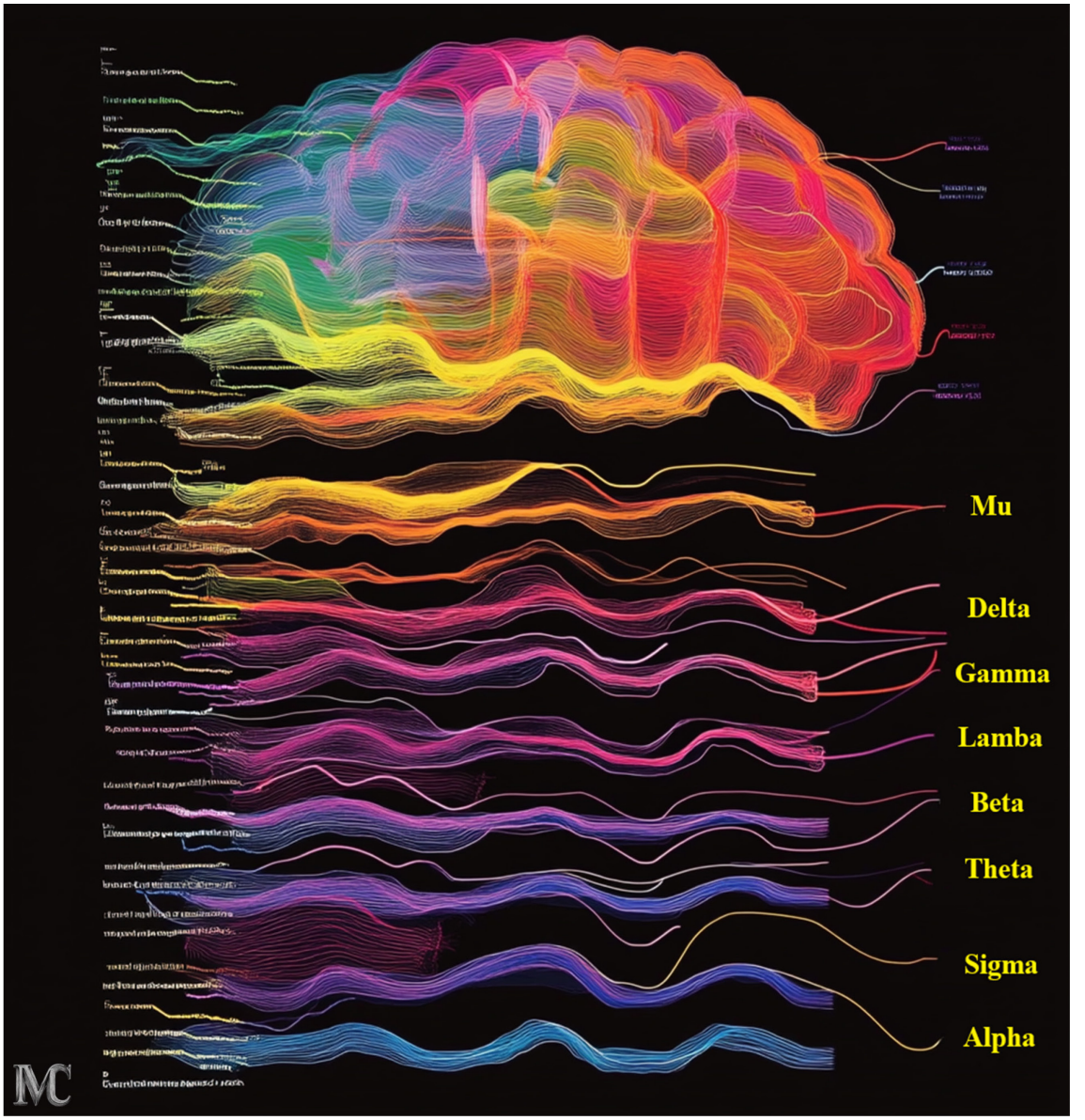
Brain Waves

Brain waves are electrical voltages that oscillate within the brain. There are five widely recognized brain waves, and three less studied types.

- Gamma associates with Memory Processing.
- Beta associates with Sensorimotor Memory.
- Alpha associates with Creativity and Perception.
- Theta associates with Long-Term Potentiation.
- Delta associates with Deep Sleep and Memory Acquisition.
- Lamba, Sigma, and Mu Waves Associate with Sensorimotor activity and visual processing, but they are far less prevalent in the human brain and therefore understudied.

Brain Waves are to be considered *the systemwide activators or nullifiers of Synapses*, and therefore memories, by changing the electrical (action potential) dynamics of neurons. It is my opinion that technologies such as Neuralink do not pose the threat of memory implantation, at least not in this lifetime, but instead of memory facilitation and dampening. Why would large corporations not mandate brain implants to stimulate brain wave patterns that would promote work efficiency, when it could save them labor costs due to enhanced work efficiency. Furthermore, the moral issue doesn't arise from the promotion of brain wave-induced cognition, but instead the loss of freedom that comes with losing the ability to control our cognitive arousal levels which is an insidious danger that certain big governments or megacorporation's will surely capitalize on to quell dissention, as integration and monitoring of brain wave patterns increases.

Psychotropic drugs, owing to the differential stimulation of neurotransmitter release, neurotrophic chemical production, and neuroreceptor binding, are liable to alter brain wave patterns, for the better, or for the worse.



By the end of this book, you will learn that Low Intensity cardio (LIT: Aerobics: Low Heart Rate, e.g. Walking) promotes memory encoding (memory acquisition), whereas High Intensity cardio (HIT: Anaerobic: High Heart Rate, e.g. Sprinting) promotes neurogenesis by way of bDNF expression, thereby resulting in increased memory consolidation. LIT does not improve memory encoding by way of neurogenesis, instead it is through altering brain oscillations, reminding us that before the Earth formed, the universe oscillated with chaotic personality, and that only through *synchronization* did we so beautifully evolve, See: ARCS, Cardio, Injuries, & Antagonist Muscle Activation.

Essential oil Volatile Organic Compounds are another effective way to alter brain wave activity in to promote calmness or alertness.

[A] Gamma oscillations appear to be of the greatest importance in restoring memory processes in damaged systems (brains).

“<>In this study, we aimed to understand how connectivity deficits lead to changes in neuronal activity patterns and the relevant neural oscillations that underlie the impaired recall of existing memories, the rescue of memory recall by slow-gamma stimulation, and impaired learning. Because it is difficult to experimentally monitor specific engram cells associated with different memories and their dynamic changes at the neuronal and synaptic levels, we conducted our study using a computationally simulated neural network model, where the degree of synaptic connectivity could be manipulated and neural firing patterns, their dynamics, and associated synaptic changes could be precisely monitored.
<>We found that reducing connectivity during memory recall caused a transition of memory-coding neurons from a synchronous state to an asynchronous state, reduced slow-gamma oscillations, and reduced neural activities associated with memory recall. Moreover, the neural activities were first increased and then reduced; suggesting that the seemingly contradictory results in circuit excitability may be induced by different degrees of connectivity impairment.
<>Second, our simulation showed that rescue using external slow-gamma stimulation at low connectivity caused a side effect of co-activating multiple memories, despite an improvement in recall performance.
<>Third, during the learning of a new memory in the presence of existing memories, our results showed that reducing connectivity induced impairment in coding the new memory engram, but did not strongly deteriorate existing memories.
<>Furthermore, our simulation suggested neuronal loss and synaptic weight reduction caused severer damage to memory performance. General increase of excitability might be an alternative measure to partially rescue memory and slightly increasing excitatory to inhibitory current ratio (E/I ratio) at low connectivity might be a remedy to memory performance caused by synaptic impairment.”[93.B]

[A2] Acetylcholine release in the Prefrontal Cortex through activation of the Nicotinic and Muscarinic Acetylcholine receptors facilitates Fast and Slow Gamma oscillations during the cognitive process of *goal-directed behavior*, thus explaining why Caffeine and Nicotine, both of which increase brain Acetycholine, are such commonly used Nootropics among our species.

“<>The capacity for using external cues to guide behavior ("cue detection") constitutes an essential aspect of attention and goal-directed behavior. The cortical cholinergic input system, via phasic increases in prefrontal acetylcholine release, plays an essential role in attention by mediating such cue detection. However, the relationship between cholinergic signaling during cue detection and neural activity dynamics in prefrontal networks remains unclear.
<>Here we combined subsecond measures of cholinergic signaling, neurophysiological recordings, and cholinergic receptor blockade to delineate the cholinergic contributions to prefrontal oscillations during cue detection in rats. We first confirmed that detected cues evoke phasic acetylcholine release. These cholinergic signals were coincident with

increased neuronal synchrony across several frequency bands and the emergence of theta-gamma coupling.
<>Muscarinic and nicotinic cholinergic receptors both contributed specifically to gamma synchrony evoked by detected cues, but the effects of blocking the two receptor subtypes were dissociable. Blocking nicotinic receptors primarily attenuated high-gamma oscillations occurring during the earliest phases of the cue detection process, while muscarinic (M1) receptor activity was preferentially involved in the transition from high to low gamma power that followed and corresponded to the mobilization of networks involved in cue-guided decision making. Detected cues also promoted coupling between gamma and theta oscillations, and both nicotinic and muscarinic receptor activity contributed to this process. These results indicate that acetylcholine release coordinates neural oscillations during the process of cue detection.
<>Significance Statement: The capacity of learned cues to direct attention and guide responding ("cue detection") is a key component of goal-directed behavior. Rhythmic neural activity and increases in acetylcholine release in the prefrontal cortex contribute to this process; however, the relationship between these neuronal mechanisms is not well understood. Using a combination of in vivo neurochemistry, neurophysiology, and pharmacological methods, we demonstrate that cue-evoked acetylcholine release, through distinct actions at both nicotinic and muscarinic receptors, triggers a procession of neural oscillations that map onto the multiple stages of cue detection. Our data offer new insights into cholinergic function by revealing the temporally orchestrated changes in prefrontal network synchrony modulated by acetylcholine release during cue detection."[93.C]

[B] Beta oscillations appear to be necessary for motor memory retrieval but not for motor memory acquisition, as Beta oscillations resynchronize post-physical activity. (PMBR: Post-Movement Beta Rebound, i.e., Restored Beta oscillations).

[1] "<>Greater post-training PMBR might reflect neural processes that facilitate practice-dependent sensorimotor reorganization after training. While beta activity, and by inference PMBR, has been suggested to promote the status quo of motor states (Engel and Fries, 2010; Gilbertson et al., 2005) and has been associated with the processing of sensory afference (Alegre et al., 2002; Cassim et al., 2001), Tan and colleagues have recently proposed a unifying theory in which PMBR is modulated by the history of task-relevant errors and is related to the uncertainty associated with feedforward predictions (Tan et al., 2016, 2014).
<>An alternative explanation might thus be that greater post-training PMBR, reflecting better accuracy (or less error) during the previous training, might then preserve motor commands or forward models that require little updating. However, the current work was not designed to study the role of beta-band dynamics for error monitoring, and thus, this interpretation is purely speculative."[93.D]

[2] "<>Our result that volitionally increasing and decreasing motor cortical beta power with neurofeedback precedes slower and faster movement onset times supports the

hypothesis that beta oscillations are linked to neural patterns that slow onset of new movements. Our results add to previously reported findings of elevated beta power prior to and after well-trained movements."
"<>In vitro slice work has identified that with sufficient excitatory drive to slices of sensorimotor or motor cortex, beta frequency oscillations emerge in deep cortical layers. It is possible that the strong excitatory drive needed to stiffen muscles during an isometric contraction task, in contrast to reaching movements that require temporal coordination of antagonist muscle groups, is sufficient to generate beta oscillations by the same means described by Roopun et al. (2006) and Yamawaki et al. (2008). Further evidence for this proposed mechanism comes from computational models of driving motoneuron recruitment with pyramidal tract neurons."[93.E]

[C] Alpha oscillations relate to creative thinking.

"<>Creativity, the ability to produce innovative ideas, is a key higher-order cognitive function that is poorly understood. At the level of macroscopic cortical network dynamics, recent electroencephalography (EEG) data suggests that cortical oscillations in the alpha frequency band (8-12 Hz) are correlated with creative thinking. However, whether alpha oscillations play a functional role in creativity has remained unknown. Here we show that creativity is increased by enhancing alpha power using 10 Hz transcranial alternating current stimulation (10 Hz-tACS) of the frontal cortex. In a study of 20 healthy participants with a randomized, balanced cross-over design, we found a significant improvement of 7.4% in the Creativity Index measured by the Torrance Test of Creative Thinking (TTCT), a comprehensive and most frequently used assay of creative potential and strengths."[93.F]

[C2] Alpha oscillations exert multiple effects on the brain, from visual memory to perception.

"<>A central feature of human brain activity is the alpha rhythm: a 7–13 Hz oscillation observed most notably over occipitoparietal brain regions during periods of eyes-closed rest. Alpha oscillations covary with changes in visual processing and have been associated with a broad range of neurocognitive functions. In this article, we review these associations and suggest that alpha oscillations can be thought to exhibit at least five distinct 'characters': those of the inhibitor, perceiver, predictor, communicator and stabiliser.
<>In short, while alpha oscillations are strongly associated with reductions in visual attention, they also appear to play important roles in regulating the timing and temporal resolution of perception. Furthermore, alpha oscillations are strongly associated with top-down control and may facilitate transmission of predictions to visual cortex.
<>This is in addition to promoting communication between frontal and posterior brain regions more generally, as well as maintaining ongoing perceptual states. We discuss why alpha oscillations might associate with such a broad range of cognitive functions and suggest ways in which these diverse associations can be studied experimentally."[93.G]

[D] Theta oscillations are necessary for LTP.

"<>We report that long-term synaptic plasticity occurs in the dentate gyrus after phasic activation of entorhinal afferents in the theta-frequency range. This plasticity is proportional to the bursting ability of granule cells. LTP of the synaptic component only occurs upon temporal proximity between stimulation via the entorhinal input and increased dentate spiking activity. Effects are input-specific and require activation of both NMDA receptors and voltage-gated calcium channels. Taken together, our findings support that dentate gyrus granule cells change their firing patterns proportionally to the preceding spiking activity of afferent inputs and that synaptic plasticity occurs as a result of this.
<>The dentate gyrus is an important component of the successful acquisition of spatial information. Rats with dentate gyrus lesions show impaired learning in the Morris water maze and are also impaired in the acquisition of spatial contextual fear conditioning. Episodic memory formation is characterized by the appearance of theta oscillations in the limbic system.
<>The temporal features of theta oscillations are thus believed to enable the assembly and segregation of neuronal groups in the hippocampus and associated structures, such that information is stored. Entorhinal cortex activity, particularly in the 5–15 Hz range, maximally enhances the polysynaptic excitation of hippocampal pyramidal neurons via the dentate gyrus. The cyclic variation of excitation and inhibition during theta provides temporal windows of opportunity to selectively ignore or enhance the effectiveness of presynaptic activity. Synchronized depolarization characterizes theta rhythm in the limbic system where each theta cycle is proposed to serve as an information quantum.
<>This field depolarization involves single spikes or complex spike bursts of the place cells that fire according to the animal's spatial position. Multiunit recordings from the CA1 region have shown that compared to single spikes, bursts of spikes lead to a significantly increased synaptic effectiveness, which positively correlates with burst length. Our data support and develop these findings. Analysis of the effects of amplifying naturally-occurring single cell plasticity, on a population level, demonstrates that long-lasting changes of the fEPSP occur only in animals where a robust increase in the spectral power of theta range was evident. The EEG of these animals displayed multiple spiking events superimposed on the positive phases of theta. We found also a highly-significant correlation between field spiking activity and fEPSP plasticity."[93.H]

[E] By far the most intriguing brain wave, Delta oscillations associate with not only sleep (δ = Delta)[1], but Intellectual work (i.e. the ability to ignore non-essential environmental and mental stimuli when studying), and long lasting neural oscillatory changes after meditation[2].

[1] "<>Sleep is associated with widespread coordination of activity across a range of brain regions. However, little is known about how activity within the largest sensorimotor region of the brain, the cerebellum, is both intrinsically organized and links with higher-order structures, such as the hippocampus, during sleep. By making multisite local field

potential recordings in naturally sleeping mice, we reveal and characterize multiple sleep stage-specific physiological mechanisms linking three distinct cerebellar regions with the hippocampus.
<>Central to these physiological mechanisms is a prominent δ (<4 Hz) oscillation, which temporally coordinates both intracerebellar and cerebello-hippocampal network dynamics. Understanding this distributed network activity is important for gaining insight into cerebellar contributions to sleep-dependent processes, such as memory consolidation."[93.I]

[2] "<>The fact that delta activity is characteristic of a state in which interneurons and the thalamocortical inputs are inactive strongly suggests that power increases of delta oscillations during mental tasks have the role of inhibiting all the interferences that may affect the performance of the task."
"<>Important evidence regarding the increase in delta activity during the suppression of interference can be found in some reports involving meditation. For example, a group of Zen meditators exhibited increased delta activity primarily in the medial prefrontal cortex during rest compared to controls; this increased activity was interpreted as an inhibition of the medial prefrontal cortex, resulting in a reduction of emotional and cognitive engagement, which was described by the Zen meditators as detachment."[93.J]

Error-related Negativity & Cognitive Dissonance

Error Processing = Cognitive Dissonance / ERN.

Cognitive Dissonance is a phenomenon that describes the mental confusion & sometimes the emotional negativity (mental discomfort) that develops in individuals in response to having their ideas (previous memories) challenged, most often during learning (error correction), or debate. Although Error-related Negativity (ERN) & Cognitive Dissonance are not directly related to neural oscillations, they do involve brain voltage changes, i.e., waveforms.

Error-related Negativity describes a "negative going waveform" or negative voltage deflection that occurs in the brain when errors occur during mental processing (choice tasks), this negative voltage results in a sharp drop in dopamine levels[F2] in certain brain regions, causing psychological discomfort in favor of promoting improved reinforcement learning. ERN exerts anxiety mental discomfort in individuals through voltage deflection in the posterior medial frontal cortex, and to a lesser extent in the Anterior Cingulate Cortex.

One may ask, would *hypersensitive* ERN explain why certain *hypersensitive* individuals dread their ideas being challenged, those of whom when their ideas are challenged become unruly, or angry? It is possible that debating religious, political, or sexual beliefs creates a greater ERN-related dopamine drop than simple emotionless lab tests do, especially when the argument made against the aforementioned hypersensitive individuals' belief(s) is logically sound, that is to say, activates patterns of thought that were forgotten or suppressed, for in most arguments or debate scenarios, the people who

shun debate or consider words *violent* are the ones who experience the greatest Startle Responses[F4] i.e. a negative mood affect resulting from experiencing threatful stimuli and directly related to ERN, or hypothetically in more severe cases, such as when individuals display Moro Reflexes in response to external speech, when they begin to scream and wave their arms around, which is an infantile motor expression of discomfort when a baby loses the physical support of their mother, and the progenitor process to ERN. Generally, these individuals only experience these neurological affects after having lost the argument or debate, proving to me that they have overreactive "defensive motivation" i.e. the motivation to be defensive when facing a perceived threat[93.J1].

Pathological Error Processing may be directly related to dopaminergic dysfunction, in that dopaminergic hypofunction may predispose an individual to shun learning (intellectual work) due to greater neurobehavioral consequences of the dopamine drop that accompanies ERN, whereas dopaminergic hyperfunction has been shown to clearly reduce cognitive flexibility in individuals due to the lack of ERN, and the generation and facilitation of errored memories. There clearly is a very important need for dopaminergic balance in the brain.

Cognitive Dissonance and ERN are similar but different reactive processes in the brain, as the former may more accurately describe the generation of psychological confusion due to encountering complex, abstract, and emotional-based memory errors, versus the latter causing overt psychological discomfort and being related to singular focused analytical errors. Both processes can occur simultaneously depending on the intensity and emotional strength of the errors encountered, both processes reduce dopamine availability in the brain to varying degrees.

ERN processing develops first in the human brain during development followed later by Cognitive Dissonance processing. It may be possible to suggest that the earliest evolution of Cognitive Dissonance from ERN in ancient hominins could be explained as an adaptation to frequent ERN resulting from rapid environmental enrichment, war, and increased socio-sexual psychological dynamics that one would have had to cope with during the formation of society and of civilization, it would therefore be a protective measure the brain enacted to avoid frequent dopamine depletion by engaging in rationalization, as rationalization may be the direct evolutionary result of ERN. Although it is obvious, it must be stated that the inability to experience Error Processing is ubiquitous in the brains of sociopaths (criminals / politicians).

Interestingly, as most drugs increase dopamine production in the brain, they make us resistant to ERN, which results in cognitive inflexibility, immorality, and the facilitation of unnecessary long term suffering. But then the question presents itself; Which is worse for a society—one that has low functioning ERN or one that fears the psychological effects ERN?

Of note, poker players offer the greatest example of what I call *Cognitive Dissonance Forethought*, wherein they analyze a complex & threatening information system. In the poker community, during times of difficult decisions a player will "tank", that is to say, willingly enter into a severe form of cognitive dissonance, thinking hard about the different possibilities that may result depending on the next action they take. During this

period, although no error has been made on their part as of yet, because there is a timed turn limit, and because a great majority of poker game decisions depend on previous errors made during the game, it is necessary to mentally analyze both previous errors and *imagine future errors*. This is a cognitive skill vital to high level poker play due to the volatility and randomness of the game of poker and is precisely why when a great poker player finally calls a bet or folds after tanking for an extended period of time, he or she experiences a cessation of mental discomfort even before any further cards are dealt or the opponents hand is seen, because the possible future error (loss) has already been analyzed and rationalized, and their dopamine levels have returned to basal levels, until the cards are dealt and a new error is possibly comprehended. The functional Cognitive Dissonance displayed by the best poker players alludes to ancient man's psychological evolution, wherein one wrong social or tactical decision made could result in death.

[A] "<>Cognitive dissonance theory suggests that our preferences are modulated by the mere act of choosing. A choice between two similarly valued alternatives creates psychological tension (cognitive dissonance) that is reduced by a postdecisional reevaluation of the alternatives. We measured EEG of human subjects during rest and free-choice paradigm. Our study demonstrates that choices associated with stronger cognitive dissonance trigger a larger negative frontocentral evoked response similar to error-related negativity, which has in turn been implicated in general performance monitoring.
<>Furthermore, the amplitude of the evoked response is correlated with the reevaluation of the alternatives. We also found a link between individual neural dynamics (long-range temporal correlations) of the frontocentral cortices during rest and follow-up neural and behavioral effects of cognitive dissonance. Individuals with stronger resting-state long-range temporal correlations demonstrated a greater postdecisional reevaluation of the alternatives and larger evoked brain responses associated with stronger cognitive dissonance. Thus, our results suggest that cognitive dissonance is reflected in both resting-state and choice-related activity of the prefrontal cortex as part of the general performance-monitoring circuitry.
<>SIGNIFICANCE STATEMENT: Contrary to traditional decision theory, behavioral studies repeatedly demonstrate that our preferences are modulated by the mere act of choosing. Difficult choices generate psychological (cognitive) dissonance, which is reduced by the postdecisional devaluation of unchosen options. We found that decisions associated with a higher level of cognitive dissonance elicited a stronger negative frontocentral deflection that peaked ~60 ms after the response. This activity shares similar spatial and temporal features as error-related negativity, the electrophysiological correlate of performance monitoring. <>Furthermore, the frontocentral resting-state activity predicted the individual magnitude of preference change and the strength of cognitive dissonance-related neural activity."
<> "To the best of our knowledge, the present study is the first EEG study to directly investigate neural correlates of cognitive dissonance during the decisional process. Our ERP data suggest that choices associated with stronger cognitive dissonance trigger a

greater negative frontocentral ERN-like deflection with the maximum at 60 ms (after the choice).”[93.K]

[B] In the following study written by Michael J. Frank, Brion S. Woroch, & Tim Curran we learn that Error-related Negativity affects behavior through causing a rapid decrease in dopamine during learning, thereby facilitating reinforcement learning. Interestingly, high levels of dopamine in the brain reduce ERN.

“<>The anterior cingulate (ACC) is critically involved in demanding cognitive tasks and is most reliably activated with increasing task difficulty. Event-related potential studies have localized an ACC component called the error-related negativity (ERN), as it is typically more negative after participants make incorrect responses, compared to correct choices. A prevailing hypothesis holds that the ERN reflects ACC activity caused by dips in dopamine (DA) following incorrect responses, which is supported by evidence of these dips from animal experiments and by observations of a strikingly similar ERP component following error feedback in trial-and-error tasks (the feedback-related negativity [FRN]).
<>However, the fundamental computational nature of the ERN and its implications for behavior are still a matter of intense debate. In particular, a major competing account suggests that the ERN is an index of response or decision conflict, of which errors are simply a special case. Each of these ERN theories (error processing and conflict monitoring) accounts for some data that the other does not, suggesting that an integrative approach is in order. Here we show that the relative size of the ERN predicts the degree to which participants learn more about the negative, as compared to positive, consequences of their decisions.
<>Further, while ERN magnitude was not associated with overall response conflict, an effect of conflict was revealed that depended on the participants learning bias. Positive learners had larger ERNs when faced with high-conflict win/win decisions among two good options than during lose/lose decisions among two bad options, whereas negative learners showed the opposite pattern. Thus, we show that the ERN is not only an error detection mechanism, but that its relative magnitude actually predicts the degree to which participants learn from errors and that its indexing of conflict depends on the type of decision faced by the particular learner.
<>We employed a modified version of a reinforcement learning paradigm previously shown to be sensitive to dopaminergic manipulation. Three different stimulus pairs (AB, CD, EF) are presented in random order, and participants have to learn to choose one of the two stimuli. Feedback follows the choice to indicate whether it was correct or incorrect, but this feedback is probabilistic. A choice of stimulus A leads to visual positive feedback in 80% of AB trials, whereas a B choice leads to negative feedback in these trials (and vice versa for the remaining 20% of trials). CD and EF pairs are less reliable: stimulus C is correct in 70% of CD trials, while E is correct in 60% of EF trials. Over the course of training, participants learn to choose stimuli A, C, and E more often than B, D, or F. Note that learning to choose A over B could be accomplished either by learning that A leads to positive feedback or that B leads to negative feedback (or both). To evaluate whether participants learned more about positive or negative outcomes of

their decisions, we subsequently tested them with all novel combinations of training stimuli (e.g., AC, BD, etc.). If participants learned more from positive feedback, they should reliably choose stimulus A in all novel test pairs in which it is present. On the other hand, if they learned more from negative feedback, they should more reliably avoid stimulus B.

<>As expected, the base-to-peak ERN magnitude following erroneous test responses was larger than that of the CRN following correct choices (−3.04 μV compared with −2.29 μV, $t[48] = 4.4$, $p < 0.0001$). Notably, the ERN magnitude was predictive of the degree to which participants learned more from the negative than positive consequences of their decisions. That is, more negative ERNs were correlated with a propensity to avoid the most negative stimulus B in novel test pairs ($r = -0.46$, $p < 0.001$) and with a bias to more reliably avoid B than to choose the most positive stimulus A ($r = -0.35$, $p = 0.01$). In contrast, the CRN magnitude was not predictive of either positive ($r = -0.19$, n.s.) or negative ($r = -0.2$, n.s.) learning. Finally, relatively larger ERN than CRN magnitudes were correlated with better negative than positive learning ($r = -0.35$, $p = 0.01$).

<>Taken together, our findings provide valuable constraints toward advancing theoretical perspectives on the role of the ERN in reinforcement learning and decision making. First, our results are consistent with a large literature pointing to a role for the ERN in error detection but go beyond these studies to demonstrate that the ERN also reflects error correction. Previous attempts to link the ERN with error correction failed to show a relationship with the behavioral slowing that is typically observed following errors. We find that, rather than having an effect on response speed, larger ERNs were associated with a bias to learn to avoid negative events more than to seek positive events.

<>Second, because negative learners also had relatively larger FRNs following negative feedback, our results suggest that the FRN may index a trait or state variable associated with whether participants are more responsive to positive or negative reinforcement and provide corroboratory evidence for the hypothesis that the FRN and ERN reflect common neural processes.

<>Third, our findings shed light on competing theories of error and conflict monitoring within the ACC. While there was no overall conflict effect on ERN magnitude, positive and negative learners may have experienced differential conflict depending on whether they were making win/win or lose/lose decisions. Finally, our results provide insight into the consistent observation that both ERNs and harm avoidance are enhanced in participants with negative affect, anxiety, and depression, suggesting that increased ACC activity can lead to enhanced sensitivity to one's mistakes and subsequent avoidance behavior.

<>Despite not manipulating or measuring dopamine (DA) function directly, our findings also lend support to the general notion that ERNs are related to DA dips that occur during error processing. Specifically, our computational model of the basal ganglia suggests that dips in DA enable NoGo learning to avoid maladaptive decisions, whereas DA bursts support Go learning from positive decision outcomes. We recently confirmed a central prediction of this model by showing that Parkinson's patients, who have low levels of DA, learned more from negative than positive reinforcement. Further, dopaminergic medication reversed this bias, improving positive but impairing negative reinforcement

learning, consistent with the notion that medication increases DA levels and blocks the effects of DA dips that would normally support NoGo learning. We also observed this same crossover interaction on positive/negative learning in young, healthy participants taking low doses of two opposing DA medications."[93.K1] [Truncated]

[C] As expected, stronger Error-related Negativity responses are associated with less self-control failures. Intelligence is dependent on the ability to learn from your errors, to embrace the discomfort of being proven wrong.

"<>Adaptive behavior critically depends on performance monitoring (PM), the ability to monitor action outcomes and the need to adapt behavior. PM-related brain activity has been linked to guiding decisions about whether action adaptation is warranted. The present study examined whether PM-related brain activity in a flanker task, as measured by electroencephalography (EEG), was associated with adaptive behavior in daily life. Specifically, we were interested in the employment of self-control, operationalized as self-control failures (SCFs), and measured using ecological momentary assessment. Analyses were conducted using an adaptive elastic net regression to predict SCFs from EEG in a sample of 131 participants. The model was fit using within-subject averaged response-locked EEG activity at each electrode and time point within an epoch surrounding the response.
<>We found that higher amplitudes of the error-related negativity (ERN) were related to fewer SCFs. This suggests that lower error-related activity may relate to lower recruitment of interventive self-control in daily life. Altered cognitive control processes, like PM, have been proposed as underlying mechanisms for various mental disorders. Understanding how alterations in PM relate to regulatory control might therefore aid in delineating how these alterations contribute to different psychopathologies."[93.L]

[D] ERN is related to anxiety and increased startle responses.

"<>Identifying biomarkers that characterize developmental trajectories leading to anxiety disorders will likely improve early intervention strategies as well as increase our understanding of the etiopathogenesis of these disorders. The error-related negativity (ERN), an event-related potential that occurs during error commission, is increased in anxious adults and children-and has been shown to predict the onset of anxiety disorders across childhood.
<>The ERN has therefore been suggested as a biomarker of anxiety. However, it remains unclear what specific processes a potentiated ERN may reflect. We have recently proposed that the ERN may reflect trait-like differences in threat sensitivity; however, very few studies have examined the ERN in relation to other indices of this construct. In the current study, the authors measured the ERN, as well as affective modulation of the startle reflex, in a large sample (N = 155) of children.
<>Children characterized by a large ERN also exhibited greater potentiation of the startle response in the context of unpleasant images, but not in the context of neutral or pleasant images. In addition, the ERN, but not startle response, related to child anxiety disorder

status. These results suggest a relationship between error-related brain activity and aversive potentiation of the startle reflex during picture viewing-consistent with the notion that both measures may reflect individual differences in threat sensitivity. However, results suggest the ERN may be a superior biomarker of anxiety in children."[93.L1]

Blink-related Oscillations

Blinking plays a large role in memory acquisition and behavioral flexibility. Blink-related Oscillations (BRO) reflect changes in brain wave synchrony. Movies that depicted "brainwashing" as involving the use of apparatuses which prevent the eyes from closing during forced visual stimulation were quite prescient in their depictions. Relatedly, the flickering produced by LED and OLED screens are surely liable to cause changes to consciousness, and it would be intelligent for one to use flicker-free computer monitors to reduce the cognitive burden of monitor technology.

"<>Background: There is a significant need to monitor human cognitive performance in complex environments, with one example being pilot performance. However, existing assessments largely focus on subjective experiences (e.g., questionnaires) and the evaluation of behavior (e.g., aircraft handling) as surrogates for cognition or utilize brainwave measures which require artificial setups (e.g., simultaneous auditory stimuli) that intrude on the primary tasks. Blink-related oscillations (BROs) are a recently discovered neural phenomenon associated with spontaneous blinking that can be captured without artificial setups and are also modulated by cognitive loading and the external sensory environment-making them ideal for brain function assessment within complex operational settings.
<>Methods: Electroencephalography (EEG) data were recorded from eight adult participants (five F, M = 21.1 years) while they completed the Multi-Attribute Task Battery under three different cognitive loading conditions. BRO responses in time and frequency domains were derived from the EEG data, and comparisons of BRO responses across cognitive loading conditions were undertaken. Simultaneously, assessments of blink behavior were also undertaken.
<>Results: Blink behavior assessments revealed decreasing blink rate with increasing cognitive load ($p < 0.001$). Prototypical BRO responses were successfully captured in all participants ($p < 0.001$). BRO responses reflected differences in task-induced cognitive loading in both time and frequency domains ($p < 0.05$). Additionally, reduced pre-blink theta band desynchronization with increasing cognitive load was also observed ($p < 0.05$).
<>Conclusion: This study confirms the ability of BRO responses to capture cognitive loading effects as well as preparatory pre-blink cognitive processes in anticipation of the upcoming blink during a complex multitasking situation. These successful results suggest that blink-related neural processing could be a potential avenue for cognitive state evaluation in operational settings-both specialized environments such as cockpits, space exploration, military units, etc. and everyday situations such as driving, athletics, human-

machine interactions, etc.-where human cognition needs to be seamlessly monitored and optimized."[93.M]

Important Inflammatory Factors

(Although MAPK's are to be considered inflammatory, and damaging to the brain, muscles, and joints in high concentrations, I am not including them in this list for the sake of simplicity as they are primarily downstream factors of IL-1 & TNF-a)

Many anti-inflammatory chemicals (antioxidants) exert their positive effects by reducing *a few key inflammatory factors* such as: Nuclear factor kappa B / p38 MAPK (Cytokines), COX2, Reactive Oxygen Species (Nitric Oxide, Free Radicals), Capase-3, and Angiogenesis. Conversely, many pro-inflammatory chemicals exert their positive effects through enhancing these factors.
Although angiogenesis is more of a process than a factor, I am including it under the Pro-Inflammation umbrella, for many inflammatory chemicals promote angiogenesis.

Inflammation as explained *perfectly* by Alexei Kurakin:

"<>Radicals and antioxidants are chemical species that can act as redox-active centers and/or constituents of electron relays in living cells and organisms. Broadly defined, radicals are any species with unpaired electrons, whereas antioxidants are any species that act as electron donors for oxidizing species, yielding less reactive products in the process. Both radicals and antioxidants can be useful and harmful for the cell, depending on the circumstances. In organized molecular contexts, radicals such as reactive oxygen species, reactive nitrogen species, amino acid radicals in proteins, base radicals in nucleic acids, and carbon and hydroperoxyl radicals in lipids may play positive roles as electron donors, acceptors, and transporters.
<>In conditions of disorganization, when for example, a macromolecular complex/structure mediating organized electron transport suddenly relaxes and/or dissociates into individual components, "freed" radicals may exert their reactivity in an uncontrolled, undirected, and thus, disruptive manner. In the same way, but at the human scale, proactive members of an organization invigorate and drive the organization. As a part of a mob, they inflame chaos and destruction. It is important to realize, however, that in the context of organizational adaptation and evolution, "disruptive" and "destruction" are not necessarily negative terms. When applied to irrelevant, inadequate, or obsolete structures, destruction can be a creative and revitalizing force. In fact, self-destruction and recreation is the only way to keep on living. This fact is reflected in the myth of the Phoenix firebird, a symbol of life. <>Pertinently, conventional fire results from the rapid oxidation of a fuel (usually a hydrocarbon) by atmospheric oxygen in an uncontrolled reaction mediated by radical intermediates. The physicochemistry of combustion and flames may thus help to explain both the positive and negative aspects of antioxidants. In the same way that both excessive and insufficient quenching of a fire are

counterproductive, as the former chokes it and the latter leads to a runaway fire, too much and too little of antioxidants are detrimental for the living fire that, in the form of organized electron flow, animates and powers cells and organisms."[93.1]

The Notable Negative Inflammatory Effects of NF-κB/IL-1:

[A] NF-κB is increasingly expressed in aged skeletal muscle and contributes to myogenic impairment.

"<>Skeletal muscle is a highly regenerative tissue, but muscle repair potential is increasingly compromised with advancing age. In this study, we demonstrate that increased NF-κB activity in aged muscle fibers contributes to diminished myogenic potential of their associated satellite cells. We further examine the impact of genetic modulation of NF-κB signaling in muscle satellite cells or myofibers on recovery after damage.
<>These studies reveal that NF-κB activity in differentiated myofibers is sufficient to drive dysfunction of muscle regenerative cells via cell-non-autonomous mechanisms. Inhibition of NF-κB, or its downstream target Phospholipase A2, in myofibers rescued muscle regenerative potential in aged muscle. Moreover, systemic administration of sodium salicylate, an FDA-approved NF-κB inhibitor, decreased inflammatory gene expression and improved repair in aged muscle.
<>Together, these studies identify a unique NF-κB regulated, non-cell autonomous mechanism by which stem cell function is linked to lipid signaling and homeostasis and provide important new targets to stimulate muscle repair in aged individuals."[94]

[B] NF-κB in chronic concentrations promotes white matter loss through oligodendrocyte senescence and subsequent death.

"<>Background: Inflammaging represents an accepted concept where the immune system shifts to a low-grade chronic pro-inflammatory state without overt infection upon aging. In the CNS, inflammaging is mainly driven by glia cells and associated with neurodegenerative processes. White matter degeneration (WMD), a well-known process in the aging brain, manifests in myelin loss finally resulting in motor, sensory and cognitive impairments. Oligodendrocytes (OL) are responsible for homeostasis and maintenance of the myelin sheaths, which is a complex and highly energy demanding process sensitizing these cells to metabolic, oxidative and other forms of stress. Yet, the immediate impact of chronic inflammatory stress like inflammaging on OL homeostasis, myelin maintenance and WMD remains open.
<>Methods: To functionally analyze the role of IKK/NF-κB signaling in the regulation of myelin homeostasis and maintenance in the adult CNS, we established a conditional mouse model allowing NF-κB activation in mature myelinating oligodendrocytes. IKK2-CAPLP−CreERT2 mice were characterized by biochemical, immunohistochemical, ultrastructural and behavioral analyses. Transcriptome data from isolated, primary OLs

and microglia cells were explored by in silico pathway analysis and validated by complementary molecular approaches.
<>Results: Chronic NF-κB activation in mature OLs leads to aggravated neuroinflammatory conditions phenocopying brain inflammaging. As a consequence, IKK2-CAPLP−CreERT2 mice showed specific neurological deficits and impaired motoric learning. Upon aging, persistent NF-κB signaling promotes WMD in these mice as ultrastructural analysis revealed myelination deficits in the corpus callosum accompanied by impaired myelin protein expression. RNA-Seq analysis of primary oligodendrocytes and microglia cells uncovers gene expression signatures associated with activated stress responses and increased post mitotic cellular senescence (PoMiCS) which was confirmed by elevated senescence-associated β-galactosidase activity and SASP gene expression profile. We identified an elevated integrated stress response (ISR) characterized by phosphorylation of eIF2α as a relevant molecular mechanism which is able to affect translation of myelin proteins.
<>Conclusions: Our findings demonstrate an essential role of IKK/NF-κB signaling in mature, post-mitotic OLs in regulating stress-induced senescence in these cells. Moreover, our study identifies PoMICS as an important driving force of age-dependent WMD as well as of traumatic brain injury induced myelin defects."[94.1]

[C] IL-1B stimulates bone erosion and is associated with the development and progression of arthritis through changing the function of T-Cells (Treg cells).

"<>IL-1β is a proinflammatory mediator with roles in innate and adaptive immunity. Here we show that IL-1β contributes to autoimmune arthritis by inducing osteoclastogenic capacity in Tregs. Using mice with joint inflammation arising through deficiency of the IL-1 receptor antagonist (Il1rn–/–), we observed that IL-1β blockade attenuated disease more effectively in early arthritis than in established arthritis, especially with respect to bone erosion.
<>Protection was accompanied by a reduction in synovial CD4+Foxp3+ Tregs that displayed preserved suppressive capacity and aerobic metabolism but aberrant expression of RANKL and a striking capacity to drive RANKL-dependent osteoclast differentiation. Both Il1rn–/– Tregs and wild-type Tregs differentiated with IL-1β accelerated bone erosion upon adoptive transfer. Human Tregs exhibited analogous differentiation, and corresponding RANKLhiFoxp3+ T cells could be identified in rheumatoid arthritis synovial tissue.
<>Together, these findings identify IL-1β–induced osteoclastogenic Tregs as a contributor to bone erosion in arthritis."[94.2]

[D] NF-κB and its downstream factor IL-1B stimulate tumorigenesis.

"IL-1β signaling contributes to tumor growth and progression through activation of numerous transcription factors, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). IL-1β contributes to suppression of the immune response against the tumor by recruiting immunosuppressive cells to the tumor microenvironment.

Infiltrating MDSCs, Tregs, and tumor-associated macrophages (TAMs) contribute to the deactivation of cytotoxic T cells in the tumor microenvironment."[95]

The Notable Positive Inflammatory Effects of NF-κB/IL-1

[A] NF-kB promotes muscle hypertrophy through directing pericytes, and its ablation enhances hyperplasia.

"<>Moreover, enhanced NF-kB activity in HPPs suppressed differentiation and enhanced proliferation of co-cultured myoblasts."[96]

[B] NF-kB associates with stem cells to promote muscle regeneration.

"<>Here, we report that canonical NF-κB signaling is induced in skeletal muscle upon injury. Satellite cell-specific inducible ablation of IKKβ attenuates skeletal muscle regeneration in adult mice. Targeted ablation of IKKβ also reduces the number of satellite cells in injured skeletal muscle of adult mice, potentially through inhibiting their proliferation and survival."[97]

[C] NF-kB promotes cognitive long-term memory.

"<>Nuclear factor kappa B (NF-κB) is a transcription factor typically expressed with two specific subunits (p50, p65). Investigators have reported that NF-κB is activated during the induction of in vitro long-term potentiation (LTP), a paradigm of synaptic plasticity and correlate of memory, suggesting that NF-κB may be necessary for some aspects of memory encoding. Furthermore, NF-κB has been implicated as a potential requirement in behavioral tests of memory. Unfortunately, very little work has been done to explore the effects of deleting specific NF-κB subunits on memory. <>Studies have shown that NF-κB p50 subunit deletion (p50-/-) leads to memory deficits, however some recent studies suggest the contrary where p50-/- mice show enhanced memory in the Morris water maze (MWM). To more critically explore the role of the NF-κB p50 subunit in synaptic plasticity and memory, we assessed long term spatial memory in vivo using the MWM, and synaptic plasticity in vitro utilizing high frequency stimuli capable of eliciting LTP in slices from the hippocampus of NF-κB p50-/- versus their controls (p50+/+).
<>We found that the lack of the NF-κB p50 subunit led to significant decreases in late LTP and in selective but significant alterations in MWM tests (i.e., some improvements during acquisition, but deficits during retention). These results support the hypothesis that the NF-κ p50 subunit is required in long term spatial memory in the hippocampus."[98]

[D] Interleukin 1 Beta prevents tendon mineralization, which is a pathological process that occurs during tendon regeneration, especially after severe injury. inTPC = injured tendon-derived progenitor cell.

"<>Our results indicate that expression of Bgn and Fmod was inhibited in inTPCs by IL-1β. These actions of IL-1β would alter the microenvironment of the niche of tendon progenitors and impair the recovery of biomechanical properties of regenerating tendons. In contrast, we detected up-regulation of expression of Dcn and Mkx which is a homeobox gene involved in tendon development. Importance of Dcn in formation of tendon collagen fibers has been demonstrated by different lines of evidence. Ito et al. have reported that Mkx mutant mice have hypoplastic tendons throughout the body and smaller collagen fibril diameters; they have also indicated that Mkx plays a critical role in tendon development by regulating type I collagen production. Significance of Dcn and Mkx by IL-1β needs to be further investigated. <>Tendon mineralization can be found as a result of tendon injuries or a feature of tendinopathy. Previous studies reported that mineralization was found in 14–62% of cases following percutaneous or open repair of the Achilles tendon and is thought to be a cause of pain and tendon weakness. Our data showed that IL-1β suppressed the chondrogenic and osteogenic differentiation ability in inTPCs, indicating that IL-1β may not directly participate in tendon mineralization in injured tendons, but rather may play an inhibitory action on tendon mineralization during the inflammatory stage."[99]

[D2] More information on Tendon Mineralization.

"<>Ectopic tendon mineralization can develop following tendon rupture or trauma surgery. The pathogenesis of ectopic tendon mineralization and its clinical impact have not been fully elucidated yet. In this study, we utilized a mouse Achilles tendon injury model to determine whether ectopic tendon mineralization alters the biomechanical properties of the tendon and whether BMP signaling is involved in this condition. A complete transverse incision was made at the midpoint of the right Achilles tendon in 8-week-old CD1 mice and the gap was left open. Ectopic cartilaginous mass formation was found in the injured tendon by 4 weeks post-surgery and ectopic mineralization was detected at 8–10 weeks post-surgery. Ectopic mineralization grew over time and volume of the mineralized materials of 25-weeks samples was about 2.5 fold bigger than that of 10-weeks samples, indicating that injury-induced ectopic tendon mineralization is progressive.
<>In vitro mechanical testing showed that max force, max stress and mid-substance modulus in the 25-weeks samples were significantly lower than the 10-weeks samples. We observed substantial increases in expression of bone morphogenetic protein family genes in injured tendons 1 week post-surgery. Immunohistochemical analysis showed that phosphorylation of both Smad1 and Smad3 were highly increased in injured tendons as early as 1 week post-injury and remained high in ectopic chondrogenic lesions 4 weeks post-injury. Treatment with the BMP receptor kinase inhibitor (LDN193189) significantly inhibited injury-induced tendon mineralization.
<>These findings indicate that injury-induced ectopic tendon mineralization is progressive, involves BMP signaling and associated with deterioration of tendon biomechanical properties."[100]

[E] Interleukin 1 Beta associates with early muscle regeneration through immune activity and stem cell production.

“<>Skeletal muscle regeneration after injury is a complex process involving interactions between inflammatory microenvironments and satellite cells. Interleukin (IL)-1 is a key mediator of inflammatory responses and exerts pleiotropic impacts on various cell types. Thus, we aimed to investigate the role of IL-1 during skeletal muscle regeneration. We herein show that IL-1α/β-double knockout (IL-1KO) mice exhibit delayed muscle regeneration after cardiotoxin (CTX) injection, characterized by delayed infiltrations of immune cells accompanied by suppressed local production of proinflammatory factors including IL-6 and delayed increase of paired box 7 (PAX7)-positive satellite cells postinjury compared with those of wild-type (WT) mice.
<>A series of in vitro experiments using satellite cells obtained from the IL-1KO mice unexpectedly revealed that IL-1KO myoblasts have impairments in terms of both proliferation and differentiation, both of which were reversed by exogenous IL-1β administration in culture. Intriguingly, the delay in myogenesis was not attributable to the myogenic transcriptional program since MyoD and myogenin were highly upregulated in IL-1KO cells, instead appearing, at least in part, to be due to dysregulation of cellular fusion events, possibly resulting from aberrant actin regulatory systems. We conclude that IL-1 plays a positive role in muscle regeneration by coordinating the initial interactions among inflammatory microenvironments and satellite cells. Our findings also provide compelling evidence
that IL-1 is intimately engaged in regulating the fundamental function of myocytes.”[101]

The Notable Negative Inflammatory Effects of Reactive Oxygen Species

[A] Chronic ROS destroy neurites.

"<>Reactive oxygen species (ROS) induce neuronal cell death in a time- and concentration-dependent manner. Treatment of cultured cells with a low concentration of hydrogen peroxide induces neurite degeneration, but not cell death. Neurites (axons and dendrites) are vulnerable to ROS. Neurite degeneration (shrinkage, accumulation, and fragmentation) has been found in neurodegenerative disorders, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease. <>However, the mechanism of ROS-related neurite degeneration is not fully understood. Many studies have demonstrated the relationship between mitochondrial dysfunction and microtubule destabilization. These dysfunctions are deeply related to changes in calcium homeostasis and ROS production in neurites.
<>Treatment with antioxidant substances, such as vitamin E, prevents neurite degeneration in cultured cells. This review describes the possibility that ROS induces neurite degeneration before the induction of cell death."[102]

[B] Chronic ROS promotes muscle atrophy.

"<>Skeletal muscle atrophy occurs under various conditions, such as disuse, denervation, fasting, aging, and various diseases. Although the underlying molecular mechanisms are still not fully understood, skeletal muscle atrophy is closely associated with reactive oxygen species (ROS) overproduction. In this study, we aimed to investigate the involvement of ROS in skeletal muscle atrophy from the perspective of gene regulation, and further examine therapeutic effects of antioxidants on skeletal muscle atrophy. Microarray data showed that the gene expression of many positive regulators for ROS production were up-regulated and the gene expression of many negative regulators for ROS production were down-regulated in mouse soleus muscle atrophied by denervation (sciatic nerve injury).
<>The ROS level was significantly increased in denervated mouse soleus muscle or fasted C2C12 myotubes that had suffered from fasting (nutrient deprivation). These two muscle samples were then treated with N-acetyl-L-cysteine (NAC, a clinically used antioxidant) or pyrroloquinoline quinone (PQQ, a naturally occurring antioxidant), respectively. As compared to non-treatment, both NAC and PQQ treatment (1) reversed the increase in the ROS level in two muscle samples; (2) attenuated the reduction in the cross-sectional area (CSA) of denervated mouse muscle or in the diameter of fasted C2C12 myotube; (3) increased the myosin heavy chain (MHC) level and decreased the muscle atrophy F-box (MAFbx) and muscle-specific RING finger-1 (MuRF-1) levels in two muscle samples.
<>Collectively, these results suggested that an increased ROS level was, at least partly, responsible for denervation- or fasting-induced skeletal muscle atrophy, and antioxidants might resist the atrophic effect via ROS-related mechanisms."[103]

The Notable Positive Inflammatory Effects of Reactive Oxygen Species

[A] ROS are necessary for muscle strength.

"<>Regarding the effects of antioxidant supplementation on strength gains, six studies reported data and the results of four of them indicate that vitamin supplementation has no influence on strength gain. Within these six studies, meta-analysis was done with the three studies that employed isokinetic assessment of muscle strength. Results of the meta-analysis confirmed that supplementation is innocuous regarding this outcome. In other words, vitamin supplementation was neither positive nor negative.

<>Importantly, the studies evaluated strength in the elderly after traditional or an undulating model of periodization or used isokinetic eccentric training in adult men. Thus, it could be inferred that vitamin C and E supplementation is ineffective with respect to strength gains independent of the population (elderly/adults), and the manipulation of training variables such as type of training (traditional/eccentric), exercises, training frequency, and volume/intensity.
<>Furthermore, Paulsen and colleagues showed that upper body strength gains were significantly higher in the placebo group (+17.1 vs. +7.6 % 1 RM gain) when compared to the supplemented group in a sample of young men and women after ten weeks of a

progressive ST program. Overall, these findings indicate that beyond ineffective, vitamin C and E supplementation could even be detrimental to strength gains in a long-term basis. This is the opposite of what could be inferred from acute design studies, as well as from the logic “conclusion” that neutralizing exercise ROS production would be beneficial to performance.”[103.1]

[B] ROS in moderate concentrations are neuritogenic.

"<>Reactive oxygen species are well known for their damaging effects due to oxidation of lipids, proteins and DNA that ultimately result in cell death. Accumulating evidence indicates that reactive oxygen species also have important signaling functions in cell proliferation, differentiation, cell motility and apoptosis. Here, we tested the hypothesis whether reactive oxygen species play a physiological role in regulating F-actin structure and dynamics in neuronal growth cones. Lowering cytoplasmic levels of reactive oxygen species with a free radical scavenger, N-tert-butyl-alpha-phenylnitrone, or by inhibiting specific sources of reactive oxygen species, such as NADPH oxidases or lipoxygenases, reduced the F-actin content in the peripheral domain of growth cones.
<>Fluorescent speckle microscopy revealed that these treatments caused actin assembly inhibition, reduced retrograde actin flow and increased contractility of actin structures in the transition zone referred to as arcs, possibly by activating the Rho pathway. Reduced levels of reactive oxygen species ultimately resulted in disassembly of the actin cytoskeleton. When neurons were cultured overnight in conditions of reduced free radicals, growth cone formation and neurite outgrowth were severely impaired. Therefore, we conclude that physiological levels of reactive oxygen species are critical for maintaining a dynamic F-actin cytoskeleton and controlling neurite outgrowth."[104]

[C] ROS promote mitochondrial biogenesis 1.

"<>Oxidative stress and the generation of reactive oxygen species (ROS) can lead to mitochondrial dysfunction, DNA damage, protein misfolding, programmed cell death with apoptosis and autophagy, and the promotion of aging -dependent processes. Mitochondria control the processing of redox energy that yields adenosine triphosphate (ATP) through the oxidation of glucose, pyruvate, and nicotinamide adenine dinucleotide. Ultimately, the generation of ROS occurs with the aerobic production of ATP. Although reduced levels of ROS may lead to tolerance against metabolic, mechanical, and oxidative stressors and the generation of brief periods of ROS during ischemia-reperfusion models may limit cellular injury, under most circumstances ROS and mitochondrial dysfunction can lead to apoptotic caspase activation and autophagy induction that can result in cellular demise.
<>Yet, new work suggests that ROS generation may have a positive impact through respiratory complex I reverse electron transport that can extend lifespan. Such mechanisms may bring new insight into clinically relevant disorders that are linked to cellular senescence and aging of the body's system. Further investigation of the potential "bright side" of ROS and mitochondrial respiration is necessary to target specific

pathways, such as the mechanistic target of rapamycin, nicotinamidases, sirtuins, mRNA decoupling and protein expression, and Wnt signaling, that can impact oxidative stress-ROS mechanisms to extend lifespan and eliminate disease onset."[105]

[D] ROS promote mitochondrial biogenesis 2.

"<>The production of reactive oxygen/nitrogen species (ROS/RNS) is generally considered to increase during physical exercise. Nevertheless, direct measurements of ROS/RNS often show modest increases in ROS/RNS in muscle fibres even during intensive fatiguing stimulation, and the major source(s) of ROS/RNS during exercise is still being debated. In rested muscle fibres, mild and acute exposure to exogenous ROS/RNS generally increases myofibrillar submaximal force, whereas stronger or prolonged exposure has the opposite effect. Endogenous production of ROS/RNS seems to preferentially decrease submaximal force and positive effects of antioxidants are mainly observed during fatigue induced by submaximal contractions. Fatigued muscle fibres frequently enter a prolonged state of reduced submaximal force, which is caused by a ROS/RNS-dependent decrease in sarcoplasmic reticulum Ca(2+) release and/or myofibrillar Ca(2+) sensitivity.
<>Increased ROS/RNS production during exercise can also be beneficial and recent human and animal studies show that antioxidant supplementation can hamper the beneficial effects of endurance training. In conclusion, increased ROS/RNS production have both beneficial and detrimental effects on skeletal muscle function and the outcome depends on a combination of factors: the type of ROS/RNS; the magnitude, duration and location of ROS/RNS production; and the defence systems, including both endogenous and exogenous antioxidants."[106]

[E] ROS are angiogenic.

“<>Reactive oxygen species (ROS) are associated with multiple cellular functions such as cell proliferation, differentiation, and apoptosis. However, the direct roles of endogenous ROS production still remain to be elucidated. In this study, we found that high levels of ROS were spontaneously produced by ovarian and prostate cancer cells. This elevated ROS production was inhibited by NADPH oxidase inhibitor diphenylene iodonium (DPI) and mitochondria electron chain inhibitor rotenone in the cells. To further analyze the source of ROS production, we found that ovarian cancer cells have much higher expression of NOX4 NADPH oxidase, and that specific inhibition of NADPH oxidase subunit p47(phox) diminished ROS production.
<>To analyze the functional relevance of ROS production, we showed that ROS regulated hypoxia-inducible factor 1 (HIF-1) and vascular endothelial growth factor (VEGF) expression in ovarian cancer cells. Elevated levels of endogenous ROS were required for inducing angiogenesis and tumor growth. NOX4 knockdown in ovarian cancer cells decreased the levels of VEGF and HIF-1 alpha and tumor angiogenesis. This study suggests a new mechanism of higher ROS production in ovarian cancer cells and provides strong evidence that endogenous ROS play an important role for cancer cells to

induce angiogenesis and tumor growth. This information may be useful to understand the new mechanism of cancer cells in inducing tumorigenesis and to develop new therapeutic strategy by targeting ROS signaling in human cancer in the future."[107]

[F] ROS promote lifespan by enhancing mitochondrial processes i.e. Mitohormesis.

"<>Oxidative stress and the generation of reactive oxygen species (ROS) can lead to mitochondrial dysfunction, DNA damage, protein misfolding, programmed cell death with apoptosis and autophagy, and the promotion of aging -dependent processes. Mitochondria control the processing of redox energy that yields adenosine triphosphate (ATP) through the oxidation of glucose, pyruvate, and nicotinamide adenine dinucleotide. Ultimately, the generation of ROS occurs with the aerobic production of ATP. Although reduced levels of ROS may lead to tolerance against metabolic, mechanical, and oxidative stressors and the generation of brief periods of ROS during ischemia-reperfusion models may limit cellular injury, under most circumstances ROS and mitochondrial dysfunction can lead to apoptotic caspase activation and autophagy induction that can result in cellular demise.
<>Yet, new work suggests that ROS generation may have a positive impact through respiratory complex I reverse electron transport that can extend lifespan. Such mechanisms may bring new insight into clinically relevant disorders that are linked to cellular senescence and aging of the body's system.
<>Further investigation of the potential "bright side" of ROS and mitochondrial respiration is necessary to target specific pathways, such as the mechanistic target of rapamycin, nicotinamidases, sirtuins, mRNA decoupling and protein expression, and Wnt signaling, that can impact oxidative stress-ROS mechanisms to extend lifespan and eliminate disease onset."[107.1]

The Notable Negative Inflammatory Effects of Tumor Necrosis Factor Alpha

[A] Chronic TNF-a promotes muscle atrophy.

"<>More recently, cell culture techniques have enabled the use of longer-term protocols. In the absence of exogenous anabolic stimuli, TNF-α directly stimulates a time-dependent and concentration-dependent decrement in total muscle protein content and loss of muscle-specific proteins, including adult fast-type myosin heavy chain (MHCf) [13,14]. MHCf losses are not accompanied by a change in synthesis rate [13], suggesting TNF-α stimulates degradation of myofibrillar proteins. Accelerated protein loss can be induced using TNF-α levels that do not stimulate cell death, by either apoptosis or necrosis, and are within the range measured clinically [13,14]. The catabolic program activated under these conditions thus closely mimics the changes observed in muscles of cachectic humans (i.e. fiber atrophy without overt cell death)."[108]

[B] TNF-a inhibits neuritogenesis.

"<>In response to injury and inflammation of the CNS, brain cells including microglia and astrocytes secrete tumor necrosis factor-alpha (TNF). This pro-inflammatory cytokine has been implicated in both neuronal cell death and survival. We now provide evidence that TNF affects the formation of neurites. Neurons cultured on astrocytic glial cells exhibited reduced outgrowth and branching of neurites after addition of recombinant TNF or prestimulation of glial cells to secrete TNF. This effect was absent in neurons of TNF receptor-deficient mice cultured on prestimulated glia of wild-type mice and was reverted by blocking TNF with soluble TNF receptor IgG fusion protein. TNF activated in neurons the small GTPase RhoA. By inactivating Rho with C3 transferase, the inhibitory effect of TNF on neurite outgrowth and branching was abolished. These results suggest that glia-derived TNF, as part of an injury or inflammatory process, can inhibit neurite elongation and branching during development and regeneration."[109]

The Notable Positive Inflammatory Effects of Tumor Necrosis Factor Alpha

[A] TNF-a promotes early skeletal muscle regeneration 1.

"<>Although p38 MAPK activation is essential for myogenesis, the upstream signaling mechanism that activates p38 during myogenesis remains undefined. We recently reported that p38 activation, myogenesis, and regeneration in cardiotoxin-injured soleus muscle are impaired in TNF-alpha receptor double-knockout (p55(-/-)p75(-/-)) mice. To fully evaluate the role of TNF-alpha in myogenic activation of p38, we tried to determine whether p38 activation in differentiating myoblasts requires autocrine TNF-alpha, and whether forced activation of p38 rescues impaired myogenesis and regeneration in the p55(-/-)p75(-/-) soleus. We observed an increase of TNF-alpha release from C2C12 or mouse primary myoblasts placed in low-serum differentiation medium. A TNF-alpha-neutralizing antibody added to differentiation medium blocked p38 activation and suppressed differentiation markers myocyte enhancer factor (MEF)-2C, myogenin, p21, and myosin heavy chain in C2C12 myoblasts.
<>Conversely, recombinant TNF-alpha added to differentiation medium stimulated myogenesis at 0.05 ng/ml while inhibited it at 0.5 and 5 ng/ml. In addition, differentiation medium-induced p38 activation and myogenesis were compromised in primary myoblasts prepared from p55(-/-)p75(-/-) mice. Increased TNF-alpha release was also seen in cardiotoxin-injured soleus over the course of regeneration. Forced activation of p38 via the constitutive activator of p38, MKK6bE, rescued impaired myogenesis and regeneration in the cardiotoxin-injured p55(-/-)p75(-/-) soleus. These results indicate that TNF-alpha regulates myogenesis and muscle regeneration as a key activator of p38."[110]

[B] TNF-a promotes early skeletal muscle regeneration 2.

"<>Degenerative and regenerative roles of tumor necrosis factor alpha (TNF-alpha), a pro-inflammatory cytokine with pleiotropic functions, were investigated by using TNF receptor 1 and 2 double knockout (TNFR-DKO) and TNF-alpha antibody neutralized

mice following traumatic freeze injury to the tibialis anterior muscle. In wild-type control mice, TNF-alpha mRNA transcripts and protein increased following injury and gradually returned to control (uninjured) levels by 13 days. A reduction in MyoD mRNA expression occurred in TNF-alpha-deficient mice, although there were no visible differences in MyoD immunostaining or histological characteristics in regenerating muscles.
<>At 5 days post-injury, the reductions in isometric strength in TNFR-DKO and TNF-alpha-depleted mice did not differ from that of wild-type mice but by 13 days after injury, the TNFR-DKO and TNF-alpha-depleted mice exhibited strength deficits twice that of wild-type mice (i.e., 27-31% vs 13%). Muscle injury was also accompanied by increased expression of interleukin-6 (IL-6), but IL-6-deficient mice demonstrated MyoD expression and recovery of isometric strength similar to that of wild-type mice. These data indicate that TNF-alpha is involved in the recovery of muscle function after traumatic muscle injury, and this effect might be associated with modulation of muscle regulatory genes, including MyoD."[111]

[C] TNF-a is angiogenic.

"<>We recently demonstrated that a co-culture system of human umbilical vein endothelial cells (HUVECs) and human dental pulp stem cells (hDPSCs) could enhance angiogenesis ability in vitro. However, whether tumor necrosis factor α (TNF-α) could promote blood vessel formation during pulp regeneration remained unknown. The aim of this study was to investigate the effects of TNF-α on the formation of endothelial tubules and vascular networks in a co-culture system of hDPSCs and HUVECs. hDPSCs were co-cultured with HUVECs at a ratio of 1:5. The Matrigel assay was performed to detect the total tubule branching lengths and numbers of branches, and the Cell-Counting Kit 8 assay was performed to examine the effect of TNF-α on cell proliferation. Real-time polymerase chain reactions and western blot were used to detect vascular endothelial growth factor (VEGF) mRNA and protein expression.
<>The Matrigel assay showed significantly greater total branching lengths and numbers of branches formed in the experimental groups treated with different concentrations of TNF-α compared with the control group. The decomposition times of the tubule structures were also significantly prolonged ($P < 0.05$). Treatment with 50 ng/ml TNF-α did not significantly change the proliferation of co-cultured cells, but it significantly increased the VEGF mRNA and protein expression levels ($p < 0.05$). In addition, the migration abilities of HUVECs and hDPSCs increased after co-culture with TNF-α ($p < 0.05$). TNF-α enhanced angiogenic ability in vitro in the co-culture system of hDPSCs and HUVECs."[112]

[D] TNF-a promotes sleep.

"<>There is ample evidence from animals and humans that TNF is involved in sleep regulation. TNF biology and TNF sleep mechanisms reveal much about sleep regulation, the minimal amount of tissue required for sleep, and sleep function. Local application of

TNF to small circuits, such as cortical columns or to co-cultures of neurons and glia induces sleep-like states. The *in vivo* and *in vitro* sleep-likes states suggest that sleep is a fundamental property of very small circuits. TNF is expressed in neurons as a consequence of neuronal activity. TNF also has a role in brain plasticity, perhaps best known are its roles in synaptic scaling and glutamate receptor (AMPA) trafficking. Both sleep and plasticity are activity-dependent and thus sleep and plasticity mechanisms are linked, and at least via TNF seem inseparable from each other. This is strong evidence for a connectivity function for sleep."[113]

[E] TNF-a expression associates predominately with fast twitch fibers.

"<>Skeletal muscle is now recognized as an endocrine organ with the capacity to produce signal peptides in response to muscle contractions. Here we demonstrate that resting healthy human muscles express cytokines in a fiber type specific manner. Human muscle biopsies from seven healthy young males were obtained from m. triceps, m. quadriceps vastus lateralis and m. soleus. Type I fibers contributed (mean +/- SE) 24.0 +/- 2.5% in triceps of total fibers, 51.3 +/- 2.4% in vastus and 84.9 +/- 22% in soleus. As expected, differences in the fiber type composition were accompanied by marked differences between the three muscles with regard to MHC I and MHC IIa mRNA expression. <>Immunohistochemistry demonstrated that tumor necrosis factor (TNF)-alpha and interleukin (IL)-18 were solely expressed by type II fibers, whereas the expression of IL-6 was more prominent in type I compared to type II fibers. The fiber type specificity was found in triceps, vastus and soleus indicating that the level of daily muscle activity did not influence basal cytokine expression. The specificity of cytokine expression in different muscle fiber types in healthy young males suggests that cytokines may play specific regulatory roles in normal physiology."[113.1]

The Notable Negative Inflammatory Effects of Interleukin-6

[A] Chronically elevated Interleukin 6 induces muscle atrophy (most likely in chronically sedentary subjects).

"<>Chronic, low-level elevation of circulating interleukin (IL)-6 is observed in disease states as well as in many outwardly healthy elderly individuals. Increased plasma IL-6 is also observed after intense, prolonged exercise. In the context of skeletal muscle, IL-6 has variously been reported to regulate carbohydrate and lipid metabolism, increase satellite cell proliferation, or cause muscle wasting. In the present study, we used a rodent local infusion model to deliver modest levels of IL-6, comparable to that present after exercise or with chronic low-level inflammation in the elderly, directly into a single target muscle in vivo.
<>The aim of this study was to examine the direct effects of IL-6 on skeletal muscle in the absence of systemic changes in this cytokine. Data included cellular and molecular markers of cytokine and growth factor signaling (phosphorylation and mRNA content) as well as measurements to detect muscle atrophy. IL-6 infusion resulted in muscle atrophy

characterized by a preferential loss of myofibrillar protein (-17%). IL-6 induced a decrease in the phosphorylation of ribosomal S6 kinase (-60%) and STAT5 (-33%), whereas that of STAT3 was increased approximately twofold. The changes seen in the IL-6-infused muscles suggest alterations in the balance of growth factor-related signaling in favor of a more catabolic profile. This suggests that downregulation of growth factor-mediated intracellular signaling may be a mechanism contributing to the development of muscle atrophy induced by elevated IL-6."[114]

[B] Interleukin 6 promotes tumor growth.

"<>In the last several decades, the number of people dying from cancer-related deaths has not reduced significantly despite phenomenal advances in the technologies related to diagnosis and therapeutic modalities. The principal cause behind limitations in the curability of this disease is the reducing sensitivity of the cancer cells towards conventional anticancer therapeutic modalities, particularly in advance stages of the disease. Amongst several reasons, certain secretory factors released by the tumour cells into the microenvironment have been found to confer resistance towards chemo- and radiotherapy, besides promoting growth. Interleukin-6 (IL-6), one of the major cytokines in the tumour microenvironment, is an important factor which is found at high concentrations and known to be deregulated in cancer.
<>Its overexpression has been reported in almost all types of tumours. The strong association between inflammation and cancer is reflected by the high IL-6 levels in the tumour microenvironment, where it promotes tumorigenesis by regulating all hallmarks of cancer and multiple signaling pathways, including apoptosis, survival, proliferation, angiogenesis, invasiveness and metastasis, and, most importantly, the metabolism. Moreover, IL-6 protects the cancer cells from therapy-induced DNA damage, oxidative stress and apoptosis by facilitating the repair and induction of countersignalling (antioxidant and anti-apoptotic/pro-survival) pathways. Therefore, blocking IL-6 or inhibiting its associated signaling independently or in combination with conventional anticancer therapies could be a potential therapeutic strategy for the treatment of cancers with IL-6-dominated signaling."[115]

[C] Interleukin 6 promotes tiredness (lethargy).

"<>Patients with pathologically increased daytime sleepiness and fatigue have elevated levels of circulating interleukin-6 (IL-6). The latter is an inflammatory cytokine, which causes sickness manifestations, including somnolence and fatigue, and activation of the hypothalamic-pituitary-adrenal axis. In this study, we examined: 1) the relation between serial measurements of plasma IL-6 and quantity and depth of sleep, evaluated by polysomnography; and 2) the effects of sleep deprivation on the nyctohemeral pattern of IL-6 secretion. Eight healthy young male volunteers were sampled for 24 h twice, at the baseline state, after a normal night's sleep and after total overnight sleep deprivation. At the baseline state, IL-6 was secreted in a biphasic circadian pattern with two nadirs at 0800 and 2100 and two zeniths at 1900 and 0500 ($P < 0.01$).

<>The baseline amount of sleep correlated negatively with the overall daytime secretion of the cytokine ($P < 0.05$). Also, depth of sleep at baseline correlated negatively with the postdeprivation increase of daytime secretion of IL-6 ($P < 0.05$). Sleep deprivation changed the temporal pattern of circadian IL-6 secretion but not the overall amount. Indeed, during the post-deprivation period, the mean daytime (0800-2200 h) levels of IL-6 were significantly higher ($P < 0.05$), whereas the nighttime (2200-0600 h) levels were lower than the predeprivation values. Thus, sleep-deprived subjects had daytime oversecretion and nighttime under-secretion of IL-6; the former might be responsible for their daylong somnolence and fatigue, the latter for the better quality (depth) of their sleep.
<>These data suggest that a good night's sleep is associated with decreased daytime secretion of IL-6 and a good sense of well-being and that good sleep is associated with decreased exposure of tissues to the proinflammatory and potentially detrimental actions of IL-6. Sleep deprivation increases daytime IL-6 and causes somnolence and fatigue during the next day, whereas postdeprivation decreases nighttime IL-6 and is associated with deeper sleep."[116]

[D] Interleukin 6 promotes arthritis and autoimmunity, again, likely in unexercised subjects.

"<>Interleukin 6 (IL-6) is a pleiotropic cytokine with a pivotal role in the pathophysiology of rheumatoid arthritis (RA). It is found in abundance in the synovial fluid and serum of patients with RA and the level correlates with the disease activity and joint destruction. IL-6 can promote synovitis and joint destruction by stimulating neutrophil migration, osteoclast maturation and vascular endothelial growth factor (VEGF)-stimulated pannus proliferation. IL-6 may also be mediating many of the systematic manifestations of RA including inducing the acute-phase reaction [including C-reactive protein (CRP)], anaemia through hecipidin production, fatigue via the hypothalamic—pituitary—adrenal (HPA) axis) and osteoporosis from its effect on osteoclasts. In addition, IL-6 may contribute to the induction and maintenance of the autoimmune process through B-cell maturation and TH-17 differentiation.
<>All of the above makes IL-6 blockade a desirable therapeutic option in the treatment of RA. Following successful animal studies, a humanized anti-interleukin-6 receptor (anti-IL-6R) monoclonal antibody, tocilizumab (TCZ), entered into clinical trials and it has been shown to be an effective treatment in several large phase III clinical trials in RA with rapid and sustained improvement in disease activity, reducing radiographic joint damage and improving physical function."[117]

The Notable Positive Inflammatory Effects of Interleukin-6

[A] Interleukin 6 is vital for muscle hypertrophy as it promotes satellite cell proliferation.

"<>Skeletal muscles adapt to increasing workload by augmenting their fiber size, through mechanisms that are poorly understood. This study identifies the cytokine interleukin-6

(IL-6) as an essential regulator of satellite cell (muscle stem cell)-mediated hypertrophic muscle growth. IL-6 is locally and transiently produced by growing myofibers and associated satellite cells, and genetic loss of IL-6 blunted muscle hypertrophy in vivo. IL-6 deficiency abrogated satellite cell proliferation and myonuclear accretion in the preexisting myofiber by impairing STAT3 activation and expression of its target gene cyclin D1. The growth defect was indeed muscle cell intrinsic, since IL-6 loss also affected satellite cell behavior in vitro, in a STAT3-dependent manner. Myotube-produced IL-6 further stimulated cell proliferation in a paracrine fashion. These findings unveil a role for IL-6 in hypertrophic muscle growth and provide mechanistic evidence for the contribution of satellite cells to this process."[118]

[B] Interleukin 6 promotes cognition in youth but hampers it in old age. Lower levels of IL-6 may also promote creative thinking.

"<>Significance of interleukin 6 (IL-6) deficiency in cognitive processes was evaluated in 4- and 24-month-old C57BL/6J IL-6-deficient (IL-6 KO) and control (WT) mice in Morris water maze (MWM), holeboard test (HB) and elevated plus maze (EPM). During 3-day learning escape latency time (ELT) was longer in IL-6 KO than in WT mice, however their swimming was slower, floating longer, and path length did not differ. The comparison of ELT and the distance traveled between the first and the third learning day within each group revealed significant decrease of ELT in all groups with the highest difference in 4-month-old WT mice, and significant decrease of distance traveled only in both groups of WT mice. In a single probe trial, performed 24 h after the last learning session, there were no major differences in the absolute values of ELT, but ELT turned out to be significantly shorter in both IL-6 KO groups, when it was compared to the ELT on the last learning day, indicating on better memory retrieval. In HB test only significant increase in number of rearings in aged WT mice, and in EPM significant prolongation of open arm time and higher number of open arm entries in 4-month-old IL-6 KO mice were observed.
<>Results of HB and EPM tests showed that alterations of learning and reference memory observed in MWM were specific to cognition. Attenuation of learning ability in young adult IL-6-deficient mice assessed in MWM suggests that physiological level of IL-6 is involved in mechanisms engaged in proper memory formation, and it may also indicate on the importance of IL-6 signaling in brain development. <>Maintained on similar level in both 4- and 24-month-old IL-6 KO mice learning ability and its attenuation in 24-month-old vs 4-month-old WT mice indicates on slower age-related memory decline in mice not expressing IL-6. Better performance of IL-6 KO mice in the probe trial points to their reference memory improvement and may also indicate that IL-6 plays a role in mechanism responsible for cognitive flexibility."[119]

[C] IL-6 promotes lipolysis 1.

"<>Although IL-6 is a key modulator of immune function, it also plays a role in regulating substrate metabolism. To determine whether IL-6 affects lipid metabolism, 18

healthy men were infused for 3 h with saline (Con; n = 6) or a high dose (High-rhIL6; n = 6) or a low dose (Low-rhIL6; n = 6) of recombinant human IL-6 (rhIL-6). The IL-6 concentration during Con, Low-rhIL6, and High-rhIL6 was at a steady state after 30 min of infusion at approximately 4, 140, and 320 pg/ml, respectively.
<>Either dose of rhIL-6 was associated with a similar increase in fatty acid (FA) concentration and endogenous FA rate of appearance (R(a)) from 90 min after the start of the infusion. The FA concentration and FA R(a) continued to increase until the cessation of rhIL-6 infusion, reaching levels approximately 50% greater than Con values. The elevated levels reached at the end of rhIL-6 infusion persisted at least 3 h postinfusion. Triacylglycerol concentrations were unchanged during rhIL-6 infusion, whereas whole body fat oxidation increased after the second hour of rhIL-6 infusion. <>Of note, during Low-rhIL6, the induced elevation in FA concentration and FA R(a) occurred in the absence of any change in adrenaline, insulin, or glucagon, and no adverse side effects were observed. In conclusion, the data identify IL-6 as a potent modulator of fat metabolism in humans, increasing fat oxidation and FA reesterification without causing hypertriacylglyceridemia."[120]

[D] IL-6 promotes lipolysis 2.

"<>A recent clinical study has demonstrated that IL-6 is required to reduce visceral adipose tissue mass in response to exercise training (Wedell-Neergaard et al., 2019). However, the role of IL-6 in the activation of WAT lipolysis is still a matter of debate, as IL-6 acute treatment does not activate adipocyte lipolysis in vitro (Trujillo et al., 2004). In addition, an acute elevation of IL-6 in vivo was described to increase whole-body lipolysis due to a rise in muscle FA release, while WAT lipolysis remained unchanged (Wolsk et al., 2010)."[121]

<u>*IL-6 is suppressed by blood sugar:</u>

"<>For most of the last century, researchers have searched for a muscle contraction-induced factor that mediates some of the exercise effects in other tissues such as the liver and the adipose tissue. It has been called the 'work stimulus', the 'work factor' or the 'exercise factor'. In the search for such a factor, a cytokine, IL-6, was found to be produced by contracting muscles and released into the blood. It has been demonstrated that IL-6 has many biological roles such as: (1) induction of lipolysis; (2) suppression of TNF production; (3) stimulation of cortisol production. The IL-6 gene is rapidly activated during exercise, and the activation of this gene is further enhanced when muscle glycogen content is low.
<>In addition, carbohydrate supplementation during exercise has been shown to inhibit the release of IL-6 from contracting muscle. Thus, it is suggested that muscle-derived IL-6 fulfils the criteria of an exercise factor and that such classes of cytokines could be termed 'myokines'."[122]

The Notable Negative Inflammatory Effects of Cycooxygenase-2

[A] COX2 promotes Neurite Outgrowth at the cost of neurogenesis and increased Amyloid deposition.

"<>Cyclooxygenase (COX) synthesizes bioactive prostaglandins from arachidonic acid, and there are COX-1 and COX-2 isoforms with distinct pathophysiological functions. Recent studies demonstrated that COX-2 expression was up-regulated in the brain of patients with Alzheimer's disease. We established mouse neuroblastoma x rat glioma hybrid NG108-15 cells stably expressing human COX-2. The COX-2-expressing cells showed 3- to 4-fold increases in both COX activity and prostaglandin E(2) production. The mRNA level of amyloid precursor protein (APP) was elevated by approximately 2-fold in the COX-2-expressing cells compared with mock-transfected cells. Amyloid beta-peptide and a secreted form of APP, both derived from APP by proteolysis was also increased.
<>Interestingly, neurite outgrowth was stimulated in the COX-2-expressing cells with concomitant reduction of the cell proliferation rate. A selective COX-2 inhibitor (JTE-522) and a nonselective COX inhibitor (indomethacin) suppressed production of amyloid beta-peptide and a secreted form of APP by inhibition of APP mRNA level, suggesting that COX-2 plays important roles in the neurodegenerative processes of Alzheimer's disease."[123]

[B] COX2 promotes excitotoxicity.

"<>Primary insults to the brain can initiate glutamate release that may result in excitotoxicity followed by neuronal cell death. This secondary process is mediated by both N-methyl-D-aspartate (NMDA) and non-NMDA receptors in vivo and requires new gene expression. Neuronal cyclooxygenase-2 (COX2) expression is upregulated following brain insults, via glutamatergic and inflammatory mechanisms. The products of COX2 are bioactive prostanoids and reactive oxygen species that may play a role in neuronal survival. This study explores the role of neuronal COX2 in glutamate excitotoxicity using cultured cerebellar granule neurons (day 8 in vitro). Treatment with excitotoxic concentrations of glutamate or kainate transiently induced COX2 mRNA (two- and threefold at 6 h, respectively, $p < 0.05$, Dunnett) and prostaglandin production (five- and sixfold at 30 min, respectively, $p < 0.05$, Dunnett). COX2 induction peaked at toxic concentrations of these excitatory amino acids. Surprisingly, NMDA, L-quisqualate, and trans-ACPD did not induce COX2 mRNA at any concentration tested. The glutamate receptor antagonist NBQX (5 microM, AMPA/kainate receptor) completely inhibited kainate-induced COX2 mRNA and partially inhibited glutamate-induced COX2 ($p < 0.05$, Dunnett). Other glutamate receptor antagonists, such as MK-801 (1 microM, NMDA receptor) or MCPG (500 microM, class 1 metabotropic receptors), partially attenuated glutamate-induced COX2 mRNA. These antagonists all reduced steady-state COX2 mRNA ($p < 0.05$, Dunnett).

<>To determine whether COX2 might be an effector of excitotoxic cell death, cerebellar granule cells were pretreated (24 h) with the COX2-specific enzyme inhibitor, DFU (5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl) phenyl-2((5)H)-furanone) prior to glutamate challenge. DFU (1 to 1000 nM) completely protected cultured neurons from glutamate-mediated neurotoxicity. Approximately 50% protection from NMDA-mediated neurotoxicity, and no protection from kainate-mediated neurotoxicity was observed. Therefore, glutamate-mediated COX2 induction contributes to excitotoxic neuronal death. These results suggest that glutamate, NMDA, and kainate neurotoxicity involve distinct excitotoxic pathways, and that the glutamate and NMDA pathways may intersect at the level of COX2."[124]

The Notable Positive Inflammatory Effects of Cycooxygenase-2

[A] COX2 associates with macrophages & stem cells to promote early skeletal muscle regeneration 1. ***Note: DOMS = Elevated Intramuscular COX-2 levels***.

"<>Skeletal muscle regeneration comprises several overlapping cellular processes, including inflammation and myogenesis. Prostaglandins (PGs) may regulate muscle regeneration, because they modulate inflammation and are involved in various stages of myogenesis in vitro. PG synthesis is catalyzed by different isoforms of cyclooxygenase (COX), which are inhibited by nonsteroidal anti-inflammatory drugs. Although experiments employing nonsteroidal anti-inflammatory drugs have implicated PGs in tissue repair, how PGs regulate muscle regeneration remains unclear, and the potentially distinct roles of different COX isoforms have not been investigated. To address these questions, a localized freeze injury was induced in the tibialis anterior muscles of mice chronically treated with either a COX-1- or COX-2-selective inhibitor (SC-560 and SC-236, respectively), starting before injury.
<>The size of regenerating myofibers was analyzed at time points up to 5 wk after injury and found to be decreased by SC-236 and in COX-2(-/-) muscles, but unaffected by SC-560. In contrast, SC-236 had no effect on myofiber growth when administered starting 7 days after injury. The attenuation of myofiber growth by SC-236 treatment and in COX-2(-/-) muscles is associated with decreases in the number of myoblasts and intramuscular inflammatory cells at early times after injury. <>Together, these data suggest that COX-2-dependent PG synthesis is required during early stages of muscle regeneration and thus raise caution about the use of COX-2-selective inhibitors in patients with muscle injury or disease."[125]

[A2] COX2 associates with macrophages & stem cells to promote early skeletal muscle regeneration 2.

"<>Anti-inflammatory strategies are often used to reduce muscle pain and soreness that can result from high-intensity muscular activity. However, studies indicate that components of the acute inflammatory response may be required for muscle repair and growth. The hypothesis of this study was that cyclooxygenase (COX)-2 activity is

required for compensatory hypertrophy of skeletal muscle. We used the synergist ablation model of skeletal muscle hypertrophy, along with the specific COX-2 inhibitor NS-398, to investigate the role of COX-2 in overload-induced muscle growth in mice. COX-2 was expressed in plantaris muscles during compensatory hypertrophy and was localized mainly in or near muscle cell nuclei. Treatment with NS-398 blunted the increases in mass and protein content in overloaded muscles compared with vehicle-treated controls. <>Additionally, the COX-2 inhibitor decreased activity of the urokinase type plasminogen activator, macrophage accumulation, and cell proliferation, all of which are required for hypertrophy after synergist ablation. Expression of insulin-like growth factor-1 and phosphorylation of Akt, mammalian target of rapamycin, and p70S6K were increased following synergist ablation, but were not affected by NS-398. Additionally, expression of atrogin-1 was reduced during hypertrophy, but was also not affected by NS-398. These results demonstrate that COX-2 activity is required for skeletal muscle hypertrophy, possibly through facilitation of extracellular protease activity, macrophage accumulation, and cell proliferation."[126]

[B] COX2 is necessary for mechanical loading-induced tendon growth.

"<>Early tendon healing can be stimulated by mechanical loading and inhibited by cyclooxygenase (COX) inhibitors (nonsteroidal anti-inflammatory drugs). Therefore, we investigated if impairment of tendon healing by a COX-2 inhibitor (parecoxib) is related to loading. Because loading might infer microdamage, which also stimulates healing, we also investigated if this effect is inhibited by parecoxib. The Achilles tendon was transected in 114 rats. Three degrees of loading were used: full loading, partial unloading, and unloading (no unloading, Botox injections in the plantar flexor muscles, or Botox in combination with tail suspension). For each loading condition, the rats received either parecoxib or saline. In a second experiment, rats were unloaded with Botox, and the tendon was subjected to microdamage by needling combined with either saline or parecoxib.
<>Mechanical testing day 7 showed that there was a significant interaction between loading and parecoxib for peak force at failure ($P < 0.01$). However, logarithmic values showed no significant interaction, meaning that we could not exclude that the inhibitory effect of parecoxib was proportionate to the degree of loading. Microbleeding was common in the healing tissue, suggesting that loading caused microdamage. Needling increased peak force at failure ($P < 0.01$), and this effect of microdamage was almost abolished by parecoxib ($P < 0.01$). Taken together, this suggests that COX-2 inhibition impairs the positive effects of mechanical loading during tendon healing, mainly by reducing the response to microdamage."[127]

[C] COX2 positively participates in memory 1.

"<>The functional significance of cyclooxygenases (COX-1 and -2), the key enzymes that convert arachidonic acid (AA) to prostaglandins (PGs) in brain, is unclear, although they have been implicated in cellular functions and in some neurologic disorders,

including stroke, epilepsy, and Alzheimer's disease. Recent evidence that COX-2 is expressed in postsynaptic dendritic spines (which are specialized structures involved in synaptic signaling) and is regulated by synaptic activity implies participation of COX-2 in neuronal plasticity.
<>However, direct evidence is lacking. Here we demonstrate that selective COX-2 inhibitors significantly reduced postsynaptic membrane excitability, back-propagating dendritic action potential-associated Ca2+ influx, and long-term potentiation (LTP) induction in hippocampal dentate granule neurons, while a COX-1 inhibitor is ineffective. All of these actions were effectively reversed by exogenous application of PGE2 but not of PGD2 or PGF(2alpha). Our results indicate that COX-2-generated PGE2 regulates membrane excitability and long-term synaptic plasticity in hippocampal perforant path-dentate gyrus synapses."[128]

[C2] COX2 positively participates in memory 2.

"<>Evidence indicates that prostanoids, such as prostaglandins, play a regulatory role in several forms of neural plasticity, including long-term potentiation, a cellular model for certain forms of learning and memory. In these experiments, the significance of the COX isoforms cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) in post-training memory processes was assessed. Adult male Long-Evans rats underwent an eight-trial (30-sec intertrial interval) training session on a hippocampus-dependent (hidden platform) or dorsal striatal-dependent (visible platform) tasks in a water maze.
<>After the completion of training, rats received an intraperitoneal injection of the nonselective COX inhibitor indomethacin, the COX-1-specific inhibitor piroxicam, the COX-2-specific inhibitor N-[2-cyclohexyloxy-4-nitrophenyl]-methanesulfonamide (NS-398), vehicle (45% 2-hydroxypropyl-beta-cyclodextrin in distilled water), or saline.
<>On a two-trial retention test session 24 h later, latency to mount the escape platform was used as a measure of memory. In the hidden platform task, the retention test escape latencies of rats administered indomethacin (5 and 10 mg/kg) or NS-398 (2 and 5 mg/kg) were significantly higher than those of vehicle-treated rats, indicating an impairment in retention. Injections of indomethacin or NS-398 that were delayed 2 h post-training had no effect on retention. Post-training indomethacin or NS-398 had no influence on retention of the visible platform version of the water maze at any of the doses administered. Furthermore, selective inhibition of COX-1 via post-training piroxicam administration had no effect on retention of either task.
These findings indicate that COX-2 is a required biochemical component mediating the consolidation of hippocampal-dependent memory."[129]

[D] COX2 promotes cardiovascular health (NSAID Lawsuits incoming).

"<>Placebo-controlled trials of nonsteroidal antiinflammatory drugs (NSAIDs) selective for COX-2 have revealed an enhanced risk for cardiovascular events. COX-2 inhibitors (coxibs) selectively reduce vascular prostacyclin synthesis without disrupting COX-1-derived thromboxane synthesis in platelets. Removal of prostacyclin's capacity to restrain

all known endogenous compounds contributing to platelet activation and vasoconstriction is a well-recognized mechanism for coxib action in the cardiovascular system which can pre-dispose to thrombosis, hypertension and atherosclerosis. Novel mouse models of selective COX-2 inhibition and disruption of microsomal prostaglandin E synthase-1 have been exploited to reveal the relative importance of prostacyclin and prostaglandin E2 in cardiovascular homeostasis. This review discusses the background to our current understanding of coxibs and provides further information relating to recent mechanistic insights into how COX-2 inhibition promotes cardiovascular risk."[130]

[E] COX2 is angiogenic.

"<>Angiogenesis is required for multistage carcinogenesis. The inducible enzyme cyclooxygenase-2 (COX-2) is an important mediator of angiogenesis and tumor growth. COX-2 expression occurs in a wide range of preneoplastic and malignant conditions; and the enzyme has been localized to the neoplastic cells, endothelial cells, immune cells, and stromal fibroblasts within tumors. The proangiogenic effects of COX-2 are mediated primarily by three products of arachidonic metabolism: thromboxane A(2) (TXA(2)), prostaglandin E(2) (PGE(2)), and prostaglandin I(2) (PGI(2)). Downstream proangiogenic actions of these eicosanoid products include: (1) production of vascular endothelial growth factor; (2) promotion of vascular sprouting, migration, and tube formation; (3) enhanced endothelial cell survival via Bcl-2 expression and Akt signaling; (4) induction of matrix metalloproteinases; (5) activation of epidermal growth factor receptor-mediated angiogenesis; and (6) suppression of interleukin-12 production. <>Selective inhibition of COX-2 activity has been shown to suppress angiogenesis in vitro and in vivo. Because these agents are safe and well tolerated, selective COX-2 inhibitors could have clinical utility as antiangiogenic agents for cancer prevention, as well as for intervention in established disease alone or in combination with chemotherapy, radiation, and biological therapies."[131]

The Notable Negative Inflammatory Effect of Caspase-3

Caspase-3, which increases with age, is associated with DNA damage (especially neurodegeneration).

"<>Interleukin 1beta-converting enzyme-like proteases (caspases) are crucial components of cell death pathways. Among the caspases identified, caspase-3 stands out because it is commonly activated by numerous death signals and cleaves a variety of important cellular proteins. Studies in caspase-3 knock-out mice have shown that this protease is essential for brain development. To investigate the requirement for caspase-3 in apoptosis, we took advantage of the MCF-7 breast carcinoma cell line, which we show here has lost caspase-3 owing to a 47-base pair deletion within exon 3 of the CASP-3 gene. This deletion results in the skipping of exon 3 during pre-mRNA splicing, thereby abrogating translation of the CASP-3 mRNA. Although MCF-7 cells were still sensitive

to tumor necrosis factor (TNF)- or staurosporine-induced apoptosis, no DNA fragmentation was observed.
<>In addition, MCF-7 cells undergoing cell death did not display some of the distinct morphological features typical of apoptotic cells such as shrinkage and blebbing. Introduction of the CASP-3 gene into MCF-7 cells resulted in DNA fragmentation and cellular blebbing following TNF treatment.
<>These results indicate that although caspase-3 is not essential for TNF- or staurosporine-induced apoptosis, it is required for DNA fragmentation and some of the typical morphological changes of cells undergoing apoptosis."[131.Z]

The Notable Positive Inflammatory Effects of Caspase-3

[A] Capsase-3 enhances myogenic differentiation. Strangely, this Pro-Inflammatory molecule is essential for the transition to myoblast differentiation during myogenesis by stimulating apoptosis in myoblasts through activating the obscure factor MST1. But chronic activity Caspase-3 results in cell death, as predicted.

"<>The cellular alterations associated with skeletal muscle differentiation share a high degree of similarity with key phenotypic changes usually ascribed to apoptosis. For example, actin fiber disassembly/reorganization is a conserved feature of both apoptosis and differentiating myoblasts and the conserved muscle contractile protein, myosin light chain kinase, is required for the apoptotic feature of membrane blebbing. As such, these observations suggest that the induction of differentiation and apoptosis in the myogenic lineage may use overlapping cellular mechanisms.
<>Here, we report that skeletal muscle differentiation depends on the activity of the key apoptotic protease, caspase 3. Peptide inhibition of caspase 3 activity or homologous deletion of caspase 3 leads to dramatic reduction in both myotube/myofiber formation and expression of muscle-specific proteins. Subsequently, we have identified Mammalian Sterile Twenty-like kinase as a crucial caspase 3 effector in this cellular process. Mammalian Sterile Twenty-like kinase is cleavage-activated by caspase 3, and restoration of this truncated kinase in caspase 3 null myoblasts restores the differentiation phenotype. Taken together, these results confirm a unique and unanticipated role for a caspase 3-mediated signal cascade in the promotion of myogenesis."
"These results suggest that the endogenous activation pattern of MST1 accelerates skeletal myocyte differentiation, although potent apoptotic events can be engaged by this kinase during extended periods of activation."[131.A]

[B] Caspase-3 enhances long term memory formation.

"<>Activation of intracellular second messenger cascades has been linked to learning and memory in various organisms. Identification of down-stream targets of these second messengers that play a role in learning and memory is an active area of research. Recently, it has been reported that increases in intracellular calcium can activate a cysteine-dependent aspartate-directed protease (caspase) cascade in mice. Using an

antibody that selectively recognizes activated caspase-3, we detected the presence of this enzyme in hippocampal neurons. Inhibition of caspase activity in the hippocampus blocked long-term, but not short-term, spatial memory. These results suggest that a caspase-mediated cellular event(s) in hippocampal neurons is critical for long-term spatial memory storage."[131.B]

[C] Caspase-3, which increases in adipose tissue following TNF-a exposure, causes adipose tissue death (apoptosis). This is important information, because certain ergogenics stimulate Caspase-3 activity, such as Caffeine, and even lipolytic antioxidants such as Alpha-Lipoic acid. As to what concentration of Caspase-3 would be required to destroy a sufficient number of adipocytes, I do not know, but it must be possible at some point in time in the future to target fat pads with Caspase-3 activators to destroy fat rapidly and efficiently, at the potential cost of diabetes development.
Interestingly, Caffeine is the primary Caspase-3 activating drug most human beings utilize on a high frequency basis

"<>Regulation of fat cell number by apoptosis is proposed to be part of a normal physiological cycle in adipose growth and development. To investigate this process, cultured rat adipocytes were treated with various concentrations of tumor necrosis factor α (TNFα) and/or insulin to determine the roles of these factors in adipocyte apoptosis. The cells were analyzed by flow cytometry using a TUNEL assay. TNFα increased adipocyte apoptosis in a dose-dependent fashion.
<>TNFα-mediated apoptosis was detectable within 6 h of treatment and continued to increase with time. Decreasing media insulin concentration from 8.5 to 0.85 nM resulted in increased adipocyte apoptosis, whereas high doses of insulin protected adipocytes from TNFα-induced apoptosis.
<>TNFα-activated apoptosis was accompanied by an increase in caspase 3 activity and could be inhibited by a caspase 3-specific inhibitor. These data suggest that adipose tissue cell number is regulated, in part, by an apoptotic signaling pathway that involves TNFα, insulin, and caspase 3."[131.B2]

Inflammation Cycling

The trend is clear, Inflammation is both beneficial to cognition & musculature and detrimental, depending on the concentration and duration of inflammatory factors in the body. It is therefore justifiable to create new protocols for the maximization of muscle growth and the promotion of memory through enhancing or suppressing inflammation with phytochemicals & ergogenic chemicals. As a retort to those who argue that antioxidants have no downside, or offer greater and safer benefits, my retort:

1. As half-lives are much forgotten, most phytochemicals will steadily rise in our bloodstream over time and become cytotoxic, even vitamins are capable of cytotoxicity if their concentrations are high enough.

2. If you are consistently inhibiting exercise-induced muscular / neurological angiogenesis, inflammatory cytokines, & other pro-inflammatory factors with Anti-Inflammation supplements you will undoubtedly enhance your risk of musculoskeletal injury or atrophy.

Furthermore, considering certain Essential Nutrients, Ascorbic Acid and Tocopherol, reduce mitochondrial biogenesis, IL-6 release, and inhibit angiogenesis, this lends more evidence to the conclusion that antioxidants serve the primary role of protecting cells from oxidative stress, but that oxidative stress is necessary for exercise-induced muscle adaptation:

"<>In this double-blind, randomised, controlled trial, we investigated the effects of vitamin C and E supplementation on endurance training adaptations in humans. Fifty-four young men and women were randomly allocated to receive either 1000 mg of vitamin C and 235 mg of vitamin E or a placebo daily for 11 weeks.
<>During supplementation, the participants completed an endurance training programme consisting of three to four sessions per week (primarily of running), divided into high-intensity interval sessions [4–6 × 4–6 min; >90% of maximal heart rate (HRmax)] and steady state continuous sessions (30–60 min; 70–90% of HRmax). Maximal oxygen uptake (Inline graphic), submaximal running and a 20 m shuttle run test were assessed and blood samples and muscle biopsies were collected, before and after the intervention.
<>Participants in the vitamin C and E group increased their Inline graphic (mean ± s.d.: 8 ± 5%) and performance in the 20 m shuttle test (10 ± 11%) to the same degree as those in the placebo group (mean ± s.d.: 8 ± 5% and 14 ± 17%, respectively). However, the mitochondrial marker cytochrome c oxidase subunit IV (COX4) and cytosolic peroxisome proliferator-activated receptor-γ coactivator 1 α (PGC-1α) increased in the m. vastus lateralis in the placebo group by 59 ± 97% and 19 ± 51%, respectively, but not in the vitamin C and E group (COX4: −13 ± 54%; PGC-1α: −13 ± 29%; $P \leq 0.03$, between groups). Furthermore, mRNA levels of CDC42 and mitogen-activated protein kinase 1 (MAPK1) in the trained muscle were lower in the vitamin C and E group than in the placebo group ($P \leq 0.05$).
<>Daily vitamin C and E supplementation attenuated increases in markers of mitochondrial biogenesis following endurance training. However, no clear interactions were detected for improvements in Inline graphic and running performance.
<>Consequently, vitamin C and E supplementation hampered cellular adaptations in the exercised muscles, and although this did not translate to the performance tests applied in this study, we advocate caution when considering antioxidant supplementation combined with endurance exercise."[131.C1]

I will now layout for you my novel idea of **Inflammation Cycling © (IMC)**.
When I say "Anti-Inflammation" I equate this term to the use of Antioxidants: Chemicals that promote Neurogenesis, reduce ROS, & inhibit Angiogenesis. And when I say "Pro-Inflammation" I equate this term to the use of ergogenic chemicals that enhance Angiogenesis, but also other factors such as IL-6, COX2, NF-kB, TNF-a, etc. Though

there is a danger of tumorigenicity during the Pro-Inflammation Cycle, this belies the developing “Fountain of Youth” theory that suggests blood vessels are vital for lifespan and optimal brain-muscle health.

There will be two cycles, one Anti-Inflammation (Antioxidant) Cycle, one Pro-Inflammation (Angiogenic) Cycle, one cycle for the brain and one cycle for the body. The duration of each cycle truly depends on one’s current health status, thus for the obese, sickly, elderly, mentally unwell, or those on steroids, it is unwise to have the ratio favor the Pro-Inflammation Cycle, conversely for those who are physically weak but have a high classically quantified intelligence and have no preexisting medical conditions, it would be unwise to focus on the Anti-Inflammation Cycle.
As each cycle’s duration truly depends on subjective physical and mental well-being, my only suggestion would be to not exceed four months on a Pro-Inflammation Cycle without *fully* replenishing essential vitamins and minerals, and when on the Pro-Cycle, ensuring you get routine bloodwork.

You will save your high load (50-100% 1RM) resistance training, Extreme Tempo training (eccentricity, superslow, & explosives) at any percentage, HIT / HIIT cardio workouts, and high frequency exercise splits for the Pro-Inflammation Cycle to magnify angiogenesis, myogenesis, neurogenesis, & lipolysis.
Because my Pro-Inflammation Cycle is focused on and based around angiogenesis, you should engage in frequent Occlusion Training, and upper-body, lower-body, or full-body warmups and aerobics should be performed nearly every day, to further magnify skeletal muscle angiogenesis, delay aging of the joints, and magnify muscle regeneration. As for brain neurogenesis and angiogenesis, there is HIT Cardio / HIIT Cardio (Neurogenesis / Cardiovascular Health) and High Intensity Endurance Training (Muscle & Brain Angiogenesis). There will always be the necessity of performing higher intensity and longer duration forms of cardiovascular exercise during inflammatory cycles to counteract the deleterious effects of ROS, connective tissue aging, & environmental toxins.

Conversely, on the Anti-Inflammation Cycle, as wound regeneration is slowed, you will focus on aerobics, low intensity cardio, isometrics, and Lactic Acid training, ideally always staying at or below 30% your 1RM for full ROM resistance training exercises to facilitate subtle hypertrophy and prevent muscle loss through undertraining. You will (partially) counteract antioxidant-induced delayed muscle regeneration with chronic hyperthermia and vibration therapy post-workout.

A vital primary goal of the Anti-Cycle should be to ensure that the new blood vessels you formed during the previous phase are not lost due to Vascular Deconditioning, and this is only possible by training a muscle with high volume, and numerous exercises, at the very least twice per week. Do not assume you will be able to maintain the intramuscular capillary growth by skipping your warmups and doing a dozen sets of three, six, or twelve repetitions (classical strength training).

It is possible, but I am not certain, that performing Isometrics and any form of static strength training (not Overload) with high loads while on an Anti-Cycle will allow you to bypass the inflammation-deficient suppression of myogenesis that is bound to occur and

protect your tendons from overt damage. If this is true it is because these two types of exercises cause very little muscle damage, and this means the damaged muscles require less stem cells to regenerate completely post-exercise, but they will surely not hypertrophy to the same extent.

If you intend on engaging in destructive exercise on an Anti-Cycle, you should do everything possible to stimulate a proper immune response post-exercise, such as utilizing intense Hyperthermia Therapy post-exercise, increasing your protein intake immediately following and in the days after your high load / high intensity exercise session, and by planning these destructive workouts as infrequent intermittent tests of musculoskeletal potential.

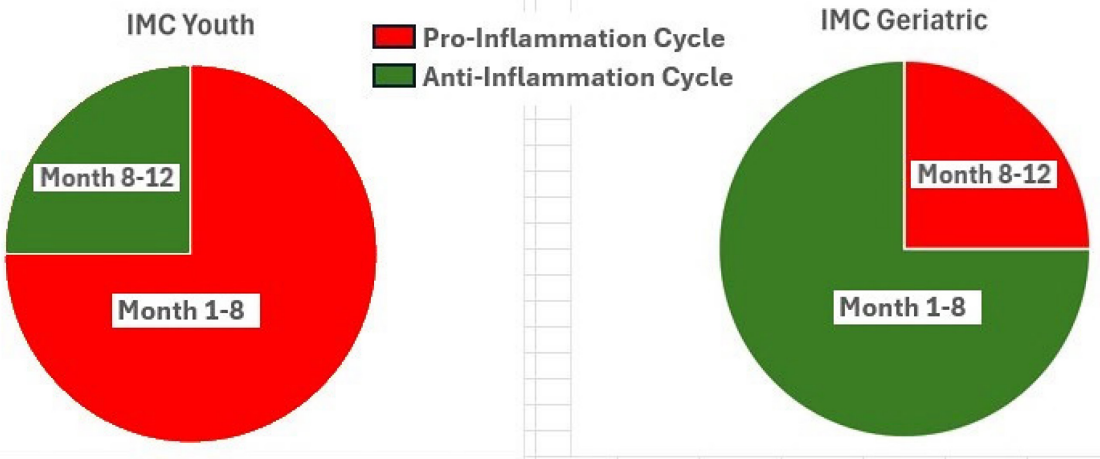
Cardiovascular Training is one of the safest ways to train hard on an Anti-Cycle due to the general reduced ROM and loads of the exercise, but jogging and running are unfortunately quite damaging to the lower hamstring muscles and are liable to cause injury if inflammation is consistently suppressed, whereas using an exercise bike, recumbent bike, or ideally a stair stepper, are relatively safe ways to overtrain the leg muscles without substantially increasing your risk for injury during periods of delayed or suppressed wound healing potential.

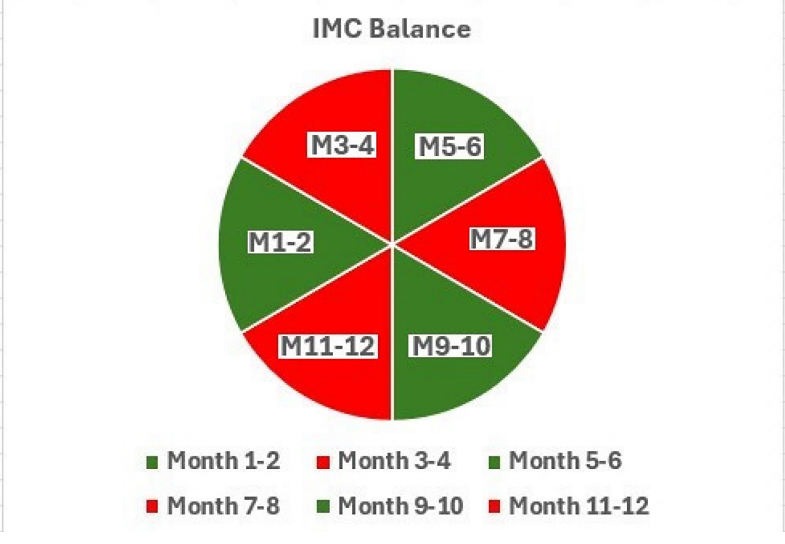
Although inflammation promotes lifespan in controlled scenarios, the progression towards cancer development is inevitable, therefore I will always suggest that older individuals focus on an anti-inflammatory cycle each year, not by taking large amounts of NSAID's, but through consuming a plethora of phytochemicals and probiotics in foods, supplements, and drinks. Unfortunately, life is not as simple as it may seem, inflammation often extends human life, depending on the amount of variables present in a human life such as exercise frequency-type-duration, environmental toxin exposure, and psychological stress levels. It is therefore essential to reinstate the importance of not blindly following one path, or one side of the inflammation coin merely because someone told you to, although I may offer guidance regarding application of these novel sciences it is up to you to choose wisely between harnessing the powers of inflammation or the powers of anti-inflammation.

If you are able to find a balance by existing in harmony between these two modes of existence, I applaud you, and will not criticize your choice, but for those who seek to capitalize on applied sciences, you have before you a new way to live through the novel biomedical philosophy of inflammatory duality.

It is true that it is an over-simplification to suggests two cycles, two modes of Inflammation, as many phytochemicals affect inflammation differently, it is still necessary to separate the processes for the sake of maximizing myogenesis, lipolysis, and neurogenesis. To condense "pro-inflammation" to predominately angiogenesis and angiogenic compounds is my idea, for when blood vessels recede, so too do physical and mental strength. The human body can thrive without IL-6, TNF-a, and COX2, but it will perish in the event that blood vessels are destroyed.

On the opposite end, Anti-Inflammation as defined by me, means Antioxidants; The multitherapy use of vitamins, phytochemicals, and even probiotics. I say *multitherapy* because many different antioxidant compounds must be used together, to reduce the many different forms of ROS, and protect DNA from damage caused by insidious environmental toxins. One antioxidant substance will not suffice for the promotion of health because the human body is assaulted daily by a seemingly innumerable number of toxic factors, each of which are liable to stimulate the production of certain ROS molecules, or dysregulate certain discrete biological processes through the promotion of inflammatory reactions. Furthermore, phytochemicals are much more complex molecules than Vitamins, and Minerals, and although many quell inflammation, they often carry with them one or more unforeseen and paradoxical pharmacodynamical effects. These effects may range from boosting Caspase-3, to causing minor DNA damage, but their pharmacodynamic benefits will not outweigh their detriments if many different antioxidant compounds, from essential, to phytochemical, are combined.





On the previous page are two visual representations of Inflammation Cycling in the form of Pie Charts that give *examples* of age-dependent IMCycling intra-calendar year, and another chart showing a good introductory IMCycling protocol focused on balance.
IMCycling timelines will always depend on myogenic goals, and current health status, making them liable to change rapidly and frequently during a person's lifetime depending on the *exigencies* of our existence.

Remember: Do not enhance inflammation (angio-potential) without both frequent long duration Steady-state cardio and infrequent high-intensity cardio to facilitate exercise-induced neuroprotection, and cardiovascular health. Also, it must be clarified that not every herb or plant on Earth is rich in antioxidants, many phytochemicals are extremely cytotoxic, and can cause organ damage, such as the recent health fad of Ashwagandha root, which has been associated with liver failure. It is safest to focus on polyphenol and vitamin supplementation before experimenting with strange classes of phytochemical compounds.

I will now detail my favorite myogenic & neurogenic (they are often synonymous) supplements for each cycle, ones I have used extensively, beginning with an explanation on fatty acids and two not often discussed amino acids (at the time of compiling and writing this book). Although this list is not exhaustive, it is more than adequate. I will not be held responsible for any medical conditions you develop through experimenting with these supplements or modalities, you will utilize them at your own risk, and only under the supervision of a licensed *Doctor*. I have included a majority of the positive and negative effects of these supplements/modalities. I will not include most of the anti-cancer or anti-angiogenic effects of Anti-Inflammation supplements—as aforementioned almost all phytochemicals kill cancer cells and inhibit angiogenesis in *high concentrations, whereas only a few exert pro-angiogenic effects in the body.

*I am referring to therapeutic concentrations. While in very low concentrations many antioxidant compounds may promote angiogenesis indirectly by reducing pathological forms of cellular stress you will have no way of knowing for certain, barring biomedical equipment, if you are forming new blood vessels while using antioxidant compounds, and therefore it is nonsensical to attempt to seek a perfect balance between antioxidants and angiogenesis while on a cycle, or protocol, that is defined by the primarily goal of the initiation and facilitation of angiogenesis. A severely ill elderly man or woman need not experiment with a Pro-Inflammation Cycle, as they will be unable to perform the requite amount of programmed cardiovascular exercise, and they will be much more liable to experience pronounced side effects, yet for those of great age who are strong, and physically active, there is no risk is short Pro-Cycles, especially for Endurance and other Cardiovascular Athletes, who possess far greater training-induced health resilience.

Dietary Fatty Acids
(A Brief Overview of Their Pharmacodynamics)

◉ There are four essential fatty acids: One Omega-6: Linoleic acid (LA). Two Omega-3's: Alpha-Linolenic acid (ALA), Docosahexaenoic Acid (DHA), & Eicosapentaenoic Acid (EPA).
◉ There are two commonly consumed non-essential fatty acids: Oleic acid (OLE), & Palmitic acid (PA).
◉ Pinolenic acid (PNLA) is a novel non-essential fatty acid found in Pine Nut oils that has antioxidant and anti-inflammatory effects.
◉ LA promotes IL-6 release & angiogenesis.
◉ ALA / DHA / EPA promote neurogenesis and exert systemic antioxidant effects.
◉ OLE exerts antioxidants effects, and also paradoxically promotes angiogenesis, but causes intramuscular lipid accumulation, and suppresses myogenesis. [See: Pro-Inflammation Cycle Dietary Fats]
◉ PA inhibits angiogenesis, causes brain / muscle lipid accumulation, and severely suppresses myogenesis.

Palmitic acid *in my opinion* is one of the leading causes of insulin resistance, brain deterioration, & muscle loss in old age. It is a saturated fat found in nearly every store-bought processed food (ice cream, pastries, cookies, nut butters, etc.), it is also found in cheese, fatty beef, and in most vegetable oils. Palmitic acid may be inflammatory, but as you will come to find—it inhibits myogenesis & angiogenesis[1], and unlike Oleic acid it is only detrimental to an athletes physical and mental performance, therefore we should avoid it if possible, alongside fructose.

The healthiest Vegetable and Seed oil are as follows:

1. Organic Hempseed oil (LA+ALA).
2. Organic Chia Seed oil (ALA: Lower PA content than Flaxseed oil).
3. *Polyphenol Concentrated Extra Virgin Olive oil (OLE) [See: Anti-Inflammation Supplementation: Oleuropein / Hydroxytyrosol]
4. Organic Pine Nut oil (PNLA).
5. Organic Grapeseed Seed oil (LA).
6. Organic Walnut oil (LA).

Oleic acid, being found at such a concentration in so many vegetable oils, including Flax / Chia Seed oil, is going to be difficult to avoid. There is no reason to avoid it when focused purely on muscle & brain angiogenesis, but excess consumption should not be part of an extended Pro-Cycle or Anti-Cycle Diet due to its inhibitory activity on myogenesis and promotion of intramuscular lipid accumulation, even though it has biological antioxidant effects. I do prefer Chia Seed oil over Flaxseed oil because I believe it is less liable to experience rancidity during manufacture, storage, and use, making it higher potency and safer.

Linoleic acid has been considered “inflammatory” and a *bad fat* for years, but it is an essential nutrient the body and brain requires to function optimally, from stimulating physiological wound healing, to protecting the brain from synaptic dysfunction. It is adipogenic, but to a much lesser extent than Palmitic acid.

If you wish to maximize lipolysis you should restrict all fatty acids, except for ALA, because fatty acids, similarly to carbohydrates, can promote adipogenesis through triglyceride generation. Even excess amounts of Coconut oil, which is considered a “fat burning” oil, can promote adiposity.

Alpha-Linolenic acid is a precursor to DHA / EPA, but it’s conversion rate to these compounds is very low, and the potent antioxidant effects of this essential fatty acid are independent of its metabolic products. It is unwise to attempt to use ALA as a proxy source of DHA / EPA if you are a vegetarian, as all that you’ll likely accomplish is flooding your body with Oleic acid (the other fatty acid present in high concentrations in high ALA plant oils).

For pleasant flavor profiles or mixed fatty acid profiles one should create *Hybrid oils* (AKA Blended oils) by mixing multiple vegetable or seed oils together. Such as Hempseed oil – Grapeseed oil – Walnut oil – Sunflower oil + EVOO for most meals, and Chia Seed oil + Pine Seed oil for sweet foods, breads, & smoothies.

The less you exercise, the less fatty acids you should consume, this is obvious to me but not to other people who insist on adding large amounts of non-essential fat rich oils to each meal under the false teaching and oversimplification that there are “good fats” and “bad fats”. Alpha-Linolenic acid is truly the only exception to this rule, as consuming it chronically even during times of inactivity won’t disturb the metabolism.

Linoleic acid, although essential, is inflammatory, but not to the degree many would purport it to be, and to restrict oils with high concentrations of it, and instead follow in step with the next big health fad, Avocado oil use, which is rich in Oleic acid, is a serious *adipogenic mistake* to make when combined with a high carbohydrate diet, especially for the elderly.

Note: There are many other non-essential fatty acids that I will not be covering, because they are either not beneficial towards human health, or unresearched, and if you choose your dietary vegetable and seed oils wisely they will be of no concern.

[1] “<>Impaired angiogenesis and wound healing carry significant morbidity and mortality in diabetic patients. Metabolic stress from hyperglycemia and elevated free fatty acids have been shown to inhibit endothelial angiogenesis. However, the underlying mechanisms remain poorly understood. In this study, we show that dysregulation of the Hippo-Yes-associated protein (YAP) pathway, an important signaling mechanism in regulating tissue repair and regeneration, underlies Palmitic Aid (PA)-induced inhibition of endothelial angiogenesis.

<>PA inhibited endothelial cell proliferation, migration, and tube formation, which were associated with increased expression of mammalian Ste20-like kinases 1 (MST1), YAP phosphorylation/inactivation, and nuclear exclusion. Overexpression of YAP or knockdown of MST1 prevented PA-induced inhibition of angiogenesis. When searching

upstream signaling mechanisms, we found that PA dysregulated the Hippo-YAP pathway by inducing mitochondrial damage. PA treatment induced mitochondrial DNA (mtDNA) release to cytosol, and activated cytosolic DNA sensor cGAS-STING-IRF3 signaling. Activated IRF3 bound to the MST1 gene promoter and induced MST1 expression, leading to MST1 up-regulation, YAP inactivation, and angiogenesis inhibition. <>Thus, mitochondrial damage and cytosolic DNA sensor cGAS-STING-IRF3 signaling are critically involved in PA-induced Hippo-YAP dysregulation and angiogenesis suppression. This mechanism may have implication in impairment of angiogenesis and wound healing in diabetes."[131.C2]

[A] A study displaying the toxicity that Palmitic acid & Oleic acid pose to myogenesis opposite to the myogenic effects of Alpha Linolenic acid.

"<>Objective: To explore the effects of different fatty acids on the proliferation and differentiation of myoblast.
<>Methods: C2C12, L6, 3T3-L1 cells were treated with different concentrations (200, 100, 50, 25 and 12.5 micromol/L) of palmitic acid (PA), oleic acid (OA) or linolenic acid (LA) for different time (2, 4, 6, 8 days), the cells proliferation were tested by MTT assay. In order to observe the effects of fatty acids on differentiation of myoblasts, C2C12 and L6 cells were treated with PA, OA or LA of 25 micromol/L at the 2 days before and 0, 2, 4 days after induced differentiation, then the oil red Ostaining, Giemsa staining and creatine kinase (CK) assay were used to determine the effects of fatty acids on cell differentiation or tans-differentiation.
<>Results: The inhibitory effect of the three kinds of fatty acids on cell proliferation and their time-dependent effects and dose-dependent effects were significantly different with changes of fatty acids and cell lines. PA and OA had more significant inhibition of cell proliferation than LA, and the inhibitory effects of OA showed no significant dose dependent for the three cell lines, while LA of below 100 micromol/L showed no significant time dependent for C2C12 and L6 myoblasts. Compared with 3T3-L1, cell proliferation of C2C12 and L6 was more sensitive to inhibitory effects of fatty acids. Fatty acid exposure after differentiation had no significant effects on differention of C2C12 and L6 myoblasts, while fatty acid exposure at 2 days before differentiation remarkably affected differentiation of the myoblasts. LA exposure could increase multinucleated myotubes and creatine kinase, and promote skeletal differentiaon of myoblasts. Conversely, PA or OA exposure induced the intracellular accumulation of lipid droplets and decreased multinucleated myotubes and creatine kinase, inhibited differentiation to skeletal cells and promoted the tans-differentiation to adipocytes of myoblast.
<>Conclusion: Fatty acids exposure affect the proliferation and differentiation of in vitro cultured myoblasts, and its function was related to fatty acid composition, cell type and exposure time."[131.D]

[B] Palmitic acid destroys Leydig cells, resulting in Testosterone deficiency in obese males. Whereas Arachidonic Acid, a fatty acid that is created through breakdown and conversion of Linoleic acid promotes Leydig cell growth.

"<>In men, obesity has generally been associated with reduced plasma testosterone levels and with elevation of the plasma free fatty acids (FFAs). In this study, we investigated the effects of saturated FFAs including palmitic acid (PA) and stearic acid (SA), and polyunsaturated FFA arachidonic acid (AA) on the survival of rat testicular Leydig cell cultured in vitro.
<>PA and SA markedly suppressed Leydig cell survival in a time- and dose-dependent manner. In contrast, AA stimulated the cell proliferation at 5-10 times of physiological concentration. The suppressive effect of PA and SA on cell survival was caused by apoptosis evidenced by DNA ladder formation and Annexin V-EGFP/propidium iodide staining of the cells.
<>The apoptotic effect of PA was possibly mediated by ceramide generation because it could be completely blocked by ceramide synthase inhibitor fumonisin B1 and exogenous ceramide itself could directly induce apoptosis in vitro. Surprisingly, the apoptosis induced by PA could be partly prevented by AA.
<>These results indicate that PA and SA induce apoptosis in testicular Leydig cells by ceramide production and these apoptotic effects may be a possible mechanism for reproductive abnormalities in obese men, and AA can partly prevent the apoptotic effect induced by saturated FFA."[131.E]

[C] Ceramide accumulation is a leading cause of neurodegeneration.

"Epidemiological studies suggest that high fat diets significantly increase the risk of Alzheimer's disease (AD). In addition, the AD brain is characterized by high fatty acid content compared to that of healthy subjects. Nevertheless, the basic mechanism relating elevated fatty acids and the pathogenesis of AD remains unclear. The present study examines the role of fatty acids in causing hyperphosphorylation of the tau protein, one of the characteristic signatures of AD pathology. Hyperphosphorylation of tau disrupts the cell cytoskeleton and leads to neuronal degeneration. Here, primary rat cortical neurons and astrocytes were treated with saturated free fatty acids (FFAs), palmitic and stearic acids. There was no change in the levels of phosphorylated tau in rat cortical neurons treated directly with these FFAs. The conditioned media from FFA-treated astrocytes, however, caused hyperphosphorylation of tau in the cortical neurons at AD-specific phospho-epitopes. Co-treatment of neurons with N-acetyl cysteine, an antioxidant, reduced FFA-induced hyperphosphorylation of tau. The present results establish a central role of FFAs in causing hyperphosphorylation of tau through astroglia-mediated oxidative stress."[131.F]

[D] Palmitic acid causes epigenetic changes in tumors and promotes tumor metastasis.

"<>Diet influences many human diseases including cancer because it changes the nutrient composition of the tumor microenvironment (TME). Tumors can utilize these nutrients such as glucose, fatty acids (FAs), or amino acids for bioenergetic and biosynthetic purposes (Altea-Manzano et al., 2020; Lien and Vander Heiden, 2019). In addition, epigenetic regulation in cancer cells and other components of the TME can promote tumor growth and metastasis formation (Carlos-Reyes et al., 2019). <>However, which diet-induced metabolic changes lead to a more aggressive epigenetic reprogramming in tumor cells is largely unexplored. The work of Pascual et al., 2021 published in Nature shows that a diet enriched in palmitic acid (PA) can reprogram cancer cells through histone methylation to acquire a more neural-like phenotype, promoting tumor innervation and metastasis formation.
<>FAs and proteins involved in FA transport have been proposed as drivers of metastasis formation (Bergers and Fendt, 2021). To understand which specific FAs support metastasis initiation, Pascual and colleagues supplemented human oral squamous cell carcinoma (OSCC) cells with PA, oleic acid (OA), and linoleic acid (LA) before orthotopic injections to mice and discovered that pretreatment with PA, but not with OA or LA, significantly increased metastasis formation without affecting primary tumor initiation.
<>PA-treated cells remained prometastatic even after 2 weeks of PA removal or subsequent OA treatment, highlighting a sustained reprogramming, i.e., a memory. Consistently, tumors isolated from mice on a palm oil diet maintained the prometastatic memory and were more metastatic even when transplanted into mice on a standard diet.
<>Importantly, induction of metastasis by PA pretreatment was dependent on the FA receptor CD36 because tumors with CD36 knockdown or treated with a CD36-neutralizing antibody showed decreased metastatic capacity despite similar primary tumor growth.
<>Because of the sustained metastatic initiation even after removing PA, the authors defined the methylation status of histones in cancer cells in the presence and absence of PA. They discovered an altered distribution of histone H3K4me3 upon PA treatment or palm oil diet that was maintained after PA removal or upon transplantation of tumors into mice on a standard diet. Interestingly, several genes with the H3K4me3 memory signature were involved in neurogenesis and neural remodeling. This suggested that PA treatment was related to tumor innervation, which is the recruitment of peripheral nerves to the TME and is a clinical sign of tumor aggressiveness (Reavis et al., 2020)."[131.G]
[E] In the study below by Massimo Cocchi, Chiara Minuto, Lucio Tonello, Fabio Gabrielli, Gustav Bernroider, Jack A Tuszynski, Francesco Cappello, & Mark Rasenick we learn that Linoleic acid (although being considered a bad inflammatory fat), is the most important fatty acid, as low brain levels associate with mental illness. Thereby explaining why some of the most psychotic or otherwise mentally unwell individuals have relatively low bodyweights. Interesting, it is suggested that Linoleic acid through its essential interaction with and protection of the cell membrane in neurons, by way of enhancing membrane fluidity, ensures the even distribution of mechanical force to Microtubules, therefore low levels of Linoleic acid in cells would be liable to promote excessive Quantum Decoherence due to pathological changes to cell membranes

(increased stiffness), and erratic mechanical forces reaching Microtubules, which would explain the many change-to-consciousness manifestations of Mental Illness that eventually lead to changes to behaviors.

After reading the article below you should find it sad how many supposed *health experts* on YouTube are warning of the dangers of Omega-6 Fatty Acids found in Seed oils, when Linoleic acid is so very important to the formation and facilitation of healthy consciousness. These supposed experts will suggest we instead use Avocado oil on all our food, that of which is loaded with Oleic & Palmitic acid.

For more information about Microtubules, See: Ion Channels: The Orchestrated Objective Reduction Theory (ORCH-OR) & Ions.

"<>We offer as the most likely explanation for the extremely low concentrations of linoleic acid, in the normal terrestrial habitat, a fortiori, the essential role such a fatty acid could play as an element that controls a symmetry breaking effect (representing a bifurcation point for the system at which two qualitatively different global behaviors can ensue) for cell membranes in the neurons and glia. This situation, involving extreme sensitivity to small, even infinitesimal changes in the control parameter values, determining the system's response in terms of its dynamical behavior, is well known in the physics of phase transitions. Near a critical state (also called a transition point) in systems undergoing phase transitions a single physical control parameter (e.g. pressure, temperature, or relative concentrations of chemical species in a mixture), determines the nature of the equilibrium state of the physical system under consideration.
<>A classic example involves a magnetic system composed of tiny magnets represented by spins arranged geometrically in a regular array. In principle they can be oriented in arbitrary directions, but they also interact with each other via nearest-neighbor coupling which is called a spin–spin interaction. For this system, there is a competition between entropy that favors disorder in the spin orientations and spin alignment along one direction due to their spin–spin coupling energy, which is minimized for parallel alignment. At high temperatures, entropy "wins" and the system is disordered. At low temperatures, the opposite happens, and the spins orient themselves along the same axis. The boundary between two ranges of temperature is called the critical point (or critical temperature) and close to a critical point very exotic behavior can be found where the system is infinitely sensitive to external stimuli such as magnetic fields and the dynamic behavior of the system's constituent spins is correlated over long distances such as small perturbations propagate from one end to the other. The two stable phases that arise are called a paramagnetic (disordered, also called symmetric) phase and a ferromagnetic (ordered, also called broken symmetry) state.
<>By analogy with the above example, we propose that linoleic acid's concentration in the membrane of neurons or glia acts as a control parameter (corresponding to temperature for magnetic systems), effectively behaving like a switch in a system close to criticality, i.e. resulting in a phase transition between a normal brain and a pathological brain when the linoleic acid concentration falls below its set value. It is important to emphasize that systems close to criticality exhibit long-range order which is important in this case so that an effect at a cell level can propagate macroscopically to the organ level,

i.e. this is not just a local effect but a global effect that involves the entire brain. The question emerges, what would this change in concentration entail regarding the dynamics of the brain, in particular the functioning of a single neuron or astrocyte? Furthermore, it is important to understand the mechanics of such an effect exerting influence on the sub-neuronal constituents such as the cytoskeleton.

<>Recent observations, conducted on the characterization of the platelet fatty acids in mood disorders and ischemic heart disease have consistently shown that a very low concentration of linoleic acid is correlated with these diseases. This observation was found to be particularly interesting in brains of depressed subjects who had completed suicide. Moreover, it seems to be supported by the work of Lalovic et al. for which, even if not significant, perhaps for a limited number of cases, it is noted that in the ventral prefrontal cortex (a decision-making area in humans) of depressed or bipolar suicidal subjects there is a slight decrease of linoleic acid, as supported by a standard deviation of the data, compared to the control groups. Together with this observation, also the results achieved of a very low concentration of linoleic acid in platelets of subjects with suicide attempts, have encouraged researchers to consider whether, in fact, it was possible to record small and significant variations of linoleic acid in other circumstances. For this purpose, a research group from the School of Agriculture and Veterinary Medicine (University of Bologna) [data not published] has recently evaluated the fatty acid compositions of the brain of obese rats. In fact, in the brains of the obese rats, there was a statistically significant reduction of linoleic acid.

<>The set of variations in the concentration of linoleic acid in the brain, undoubtedly, becomes interesting from the perspective of interpretation regarding its position in the membrane and the likelihood that these minor changes can result in the connections that the membrane makes to the cytoskeleton through the interactions with the G protein, Gsα and ion channels. A mechanistic model of this interaction could be built starting with the fatty acids in the membrane forming an ordered network whose structure depends on the specific composition of the fatty acids, in particular the linoleic acid. To embark on developing such a model we first discuss how lessons from the physics of phase transitions can help us understand the possible consequences for neuroscience."

↓ continued

"<>The state of continual renewal and exchange of fatty acids by the membrane with consequent deformation of the lipid bilayer, can be thought of in terms of a mechanical force, in both physiological and pathological conditions, which is exercised on the cytoskeleton with continuity allowing, when there are physiological conditions for the membrane, periods of decoherence of microtubules (500 ms), which give rise to the conscious manifestation which will result in classic neurocorrelate of consciousness. The problem that arises is to understand how, under different conditions of mood disorders, the decoherence can be modified by lengthening or shortening the period (< or >500 ms). Having had the opportunity to understand that a higher mobility of membrane characterizes MDD and lower, BD, it is perceived that there are pathological conditions of deformation of the membrane that may exert different mechanical forces on the cytoskeleton from the inside of the same membrane and could potentially affect the

physiological phenomenon of superposition of microtubules and consequently the period of oscillation.
<>In the case of BD there would be a shortening of the period of decoherence while in the case of MDD, an elongation. This eventuality could correspond, in cases of extreme criticality of decoherence period, to deep and decisive changes in the conscious state.
<>Having shown that between MDD and BD there is a symmetry break, keeping in mind the characteristics of mobility of the membrane, that there is a "domain wall" governed by electromagnetic forces that are likely to be the only form of communication between the two phenomena (MDD and BD) and that the only commonality of the two conditions is suicide, it seems consistent to think that such an event can take place for critical lengthening or shortening of the periods of decoherence, and, therefore, of the capacity of consciousness. These neuron forces, or "neuromechanics", could represent, the element conditioning the control domain of the microtubules and conditioning their relationship with the criticality of synapses, cortex and serotonin."[131.2]

[F] Stearic Acid, a saturated fat found in Cocoa Butter, Lard, and Butter, similarly to Palmitic acid, inhibits Endothelial Cell growth.

"<>Background & aims: Saturated fatty acids (SFAs), significant components of enteral and parenteral formulations, have been linked to cardiovascular complications. However, the effect of SFAs upon vascular inflammation is less clear. Endothelial cells (EC) play an important role in the acute inflammatory responses. We, therefore, evaluated the acute effects of different chain-length SFAs upon EC functions.
<>Methods: Endothelial cells were cultured with various SFAs. Growth and cytotoxicity were determined by WST-1 assay. Apoptosis and pro-inflammatory adhesion molecule (ICAM-1) expression was assayed using flow cytometry. Activation of NF-kappaB was analyzed using western blot analysis.
<>Results: Long-chain SFAs (C14:0-C20:0) inhibited EC growth in a chain-length dependent manner. Medium-chain SFAs (C6:0-C12:0) did not significantly affect EC growth. In contrast, the short-chain SFA (C4:0) stimulated cellular growth. Stearic acid induced significantly more EC apoptosis and necrosis than palmitic acid or myristic acids. Stearic acid (>10muM) treatment also significantly increased ICAM-1 expression. Stearic acid's pro-inflammatory response was confirmed by phosphorylation of IkappaB-alpha and NF-kappaB in a dose dependent manner.
<>Conclusions: Long-chain SFAs can induce pro-inflammatory responses and significantly impact growth and viability of EC. Our data suggest that the presence of long-chain SFAs in parenteral formulations may have harmful effects on the vascular system."[131.2.1]

[G] Pinolenic acid (PNLA) is a relatively obscure beneficially bioactive fatty acid that is found in Pine Nut oils. We learn in the article snippet below courtesy of Rabaa Takala, Dipak P. Ramji, and Ernest Choy that Pine nuts from the pine tree species P. koraiensis (Korean pine) and P. sibirica (Siberian pine) contain large concentrations of PNLA.

Pinolenic acid has been shown to increase antioxidant defenses in the body by way of SOD / GSH-Px, and to suppress weight gain, and reduce appetite.

Strangely, although Pinolenic acid converts to y-Linolenic Acid, a precursor fatty acid to Arachidonic Acid, which stimulates COX-2 activity, it appears to compete with Linoleic acid in our cells thereby reducing inflammation in the process.
(PNO = Pine Nut oil)

"<>Pine nuts and PNO consumption have increased over the last few decades. The biggest distributors are in Asia, including China, North Korea and Pakistan. Korea, the USA, and Russia are the biggest users of pine nuts and PNO. Pine nuts have a unique flavour with very high caloric and lipid content. Pine nuts are comprised of almost 64% fat, 20% protein and 5% carbohydrate. Most of the FAs in pine nuts are unsaturated FAs (UFAs) with only 10% saturated FAs (SFAs). The pine nuts are 9–12 mm long and have a high oil content (45–65 g/100 g of nuts).
<>PNLA is an unusual and unique PUFA that is found only in PNO such as Pinus orientalis and maritime pine (P. pinaster) seeds, which are rich sources of PNLA. Pine nuts from P. koraiensis (Korean pine), P. sibirica (Siberian pine), P. gerardiana (chilgoza pine) and P. pinea (stone pine) are the most common genera eaten by consumers. The nut oils from P. eldarica, P. excelsa, P. pinea and P. torreyana have low level of PNLA (very low in the case of P. pinea) and are rich in LA or oleic acid. PNO also contains antioxidant lipid-soluble components, including tocopherols, phytosterols and squalene."
"Korean pine nuts (KPN) and Siberian pine nuts (SPN) are rich sources of PNLA which forms up to 20% and 27%, respectively, of their total content."
↓ continued
"<>Dietary antioxidants may improve chronic diseases by reducing oxidative damage. Antioxidant enzymes are essential for cell defense against the harm that free radicals may do to cells and macromolecules. Two of these enzymes are phospholipid hydroperoxide glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD). P. koraiensis oil was included in a meal given to rats, and they showed elevated blood levels of SOD and GSH-Px activity. Malondialdehyde (MDA) is a sign of lipid degradation caused by free radicals and is commonly used as a biomarker for measuring lipid peroxidation in cell membranes. There was a reduction in serum MDA levels in the PNO-fed group relative to the control.
<>Additionally, in comparison to the controls, the pine high-fat diet (PHFD) group had the greatest level of SOD2 mRNA compared to PNO and soybean oil (SBO)-fed groups and soybean high-fat diet (SHFD) groups, which might shield from damage due to ROS. In H2O2-induced HepG2 cells, 1, 5, and 10 μM of PNLA, dose-dependently reduced intracellular ROS accumulation by 29.1, 59.1, and 65.5% and intracellular MDA content by 15.96%, 20.5%, and 22.9%, respectively. These data suggest that PNLA reduces ROS-induced lipid peroxidation, thereby decreasing oxidative damage. Although Takala et al. found that PNLA (25–100 μM) has no effect on ROS in THP-1 monocytes and macrophages in vitro, they found that 25 μM PNLA reduced NO production by PBMCs (unpublished observation). NO is considered one of the oxidative stress mediators."
↓ continued

"<>In various studies where mice are given HFDs containing PNO, there was weight reduction and less weight gain. White adipose tissue mass was decreased because of these alterations, most likely as a result of increased oxidative metabolism and thermogenesis, which drives the utilization of fuel sources and reduces lipid accumulations. Therefore, the effect of PNO and PNLA on weight could be the result of both increased energy expenditure and decreased intake.
<>Earlier in 2008, Hughes et al. reported a rise in the satiety hormones glucagon-like peptides (GLP-1) and cholecystokinin (CCK-8), in postmenopausal obese women participating in a pilot double-blind placebo-controlled clinical trial when taking 3 g Korean pine nuts (KPN)-FFA in comparison with 3 g KPN-TG or 3 g olive oil. The levels of circulating CCK-8 in the PNO FFA and PNO TAG groups, respectively, were 60% and 22% higher. Comparing the PNO FFA group to the control, GLP-1 rose by 25%. Food intake also diminished by 36% in the PNO FFA group suggesting that pine nuts may also be an appetite suppressant."[131.2.2]

[G2] Korean Pine Nut oil reduces adipogenesis and intramuscular lipid accumulation in mice fed a high fat diet by increasing AMPK, UCP1, & PPAR Alpha and PPAR Delta, meaning PNLA improves slow twitch fiber function and growth to accelerate metabolism.

"<>In this study, we investigated effects of pine nut oil (PNO) on high-fat-diet (HFD)-induced obesity and metabolic dysfunction in skeletal muscle and brown adipose tissue (BAT). Male C57BL/6 mice were fed a HFD with 15% energy from lard and 30% energy from either soybean oil (SBO-HFD) or PNO (PNO-HFD) for 12 weeks. The PNO-HFD resulted in less weight gain and intramuscular lipid accumulation than the SBO-HFD and was accompanied by upregulation of transcripts and proteins related to oxidative metabolism and phosphorylation of AMP-activated protein kinase (AMPK), as well as molecules selectively expressed in type I and type IIa muscle fibers.
<>In addition, uncoupling protein-1 was upregulated in BAT. These beneficial metabolic effects were partly associated with the dual ligand activity of pinolenic acid, which is abundant in PNO, for peroxisome proliferator-activated receptors α and δ. Our findings suggest that PNO may have potential as a dietary supplement for counteracting obesity and metabolic dysregulation."[131.2.3]

[See: Alpha-Linolenic Acid / MCT oil: Anti-Inflammation Cycle Dietary Fats]

[See: Linoleic Acid: Pro-Inflammation Cycle Dietary Fats]

[See: Lipolytic Supplementation: Conjugated Linoleic acid]

[See: Adipocytes, Adipogenesis, Lipolysis, & Macronutrients]

GlySer: Two Amino Acids Key to Efficient Myogenesis

Glycine & Serine: 2:1 Ratio.
I refer to a mixture of these amino acids as "***GlySer***".

These two amino acids are essential for myogenic stem cell proliferation, making them, in combination, a more important supplement to athletes than any other. Serine is the precursor to Glycine with the conversion rate being anywhere between 20-40%, with the remaining Serine being utilized in protein synthesis, making both amino acids essential.

Ideally, GlySer will be used in two different modes each day, the first is the most important, and this is post-workout, predominately anabolic workouts such as strength or powertraining, or high intensity interval cardiovascular training, where you will consume a large *acute* dosage of GlySer immediately after completing your training to rapidly stimulate mTOR. The second mode of administration will be chronic, where you will add GlySer to a drink such as Coffee, Tea, Lemonade, or Plant Milk to thereby create a "Myogenic Drink", which will be sipped *all day*, every hour or two, to maintain adequate blood levels of Glycine and Serine. You may also add GlySer to Myogenic Desserts that

are portioned out into many equally spaced out & timed meals per day, such as Homemade Oatmeal, Pudding, Cookies, Breads, or Protein Bars to name a few. If you do not train intensely twice a day, nor suffer from joint deterioration, or musculoskeletal injuries, you may not require the second mode (chronic administration) of GlySer, be aware of this.

The obvious downside to incorporating these raw amino acids into your diet will result from the second of mode of administration, and predominately Glycine, as with high concentrations consumed you may experience unexpected sleepiness, or mood changes, albeit the biggest issue that will present itself is the financial burden. When you experience daytime sleepiness from Glycine, it is not a bad thing, consider it a blessing to be able to take frequent naps which will only accelerate wound healing and memory consolidation.

It is important to mention that Serine & Glycine will promote systemic aging through increasing mTOR expression, but this will not be of concern to athletes or serious lifters, as chronic exercise (predominately cardio) will counteract mTOR's deleterious effect on cellular aging in healthy individuals. Although after a certain age, potentially fifty or sixty years old, *if you are healthy, enhancing mTOR expression chronically is not the best idea as it will accelerate myogenic stem cell senescence, making it necessary once reaching old age to transition from a focus on *cellular growth* to one of *cellular conditioning*, at the very least for the majority of each calendar year, where there can be one month or two months allocated for GlySer use, during periods of the most intense anabolic physical training.

If you are sedentary more often than not, consuming large amounts of GlySer is a bad idea, even for the promotion of skin, brain, and joint health, as you will unnecessarily shorten your lifespan. That is not to say I am totally against the use of Glycine in sedentary individuals, as it is an excellent and essential sleep aid and will delay the aging of our joints.

GlySer can be consumed during either cycle but be aware that Glycine in higher dosages shows anti-angiogenic activity, therefore you should avoid supplementing it during my Pro-Inflammation (Angiogenic) Cycle.

There is no doubt you could consume adequate amounts of these intriguing amino acids in commonly available unadulterated protein powders, especially ones that are mixed together, if the amount consumed is high enough each workout (Example: 50-70g Whey Isolate Pre-Workout), and this may be the best option for those with neurological conditions, or budget restrictions, but isolated bulk powders are the best option for those who train hard, and often.

If you experience severe negative changes to mood or memory (See [E]-[F]-[G]) after acute GlySer (Glycine) use, you're likely experiencing excitotoxicity, because Glycine is both inhibitory and excitatory. Try to reduce the dosing of GlySer to an inverted 1:2 (Glycine - Serine) ratio, or plan your most strenuous exercise sessions for the evening and only consume Glycine after these workouts (before bed), or simply eliminate Glycine altogether from your supplement protocol while experimenting with higher dosages of Serine. The final studies listed in this section highlight the dangers of *excess* or *chronic*

Glycine use, do please pay attention, and remember that your muscles are not worth more than your brain.

Collagen powders, which are good sources of Glycine, are unfortunately overpriced as compared to singular sources that are sold in bulk on the internet, and are likely to contain contaminants such as heavy metals.

*I say "*if you are healthy*" because, in scenarios of sickness (not cancer), suppressing mTOR or the AKT pathway (Insulin) may promote further apoptosis in muscle cells, or neurons, as both mTOR and Insulin are antiapoptotic, therefore a strange conundrum forms. If you are healthy at any age, restricting Insulin release, or mTOR, may delay aging, but if you are physically weak, or neurologically unwell, it may do more harm than good to fast, or to restrict essential amino acids, and insulinemic carbohydrates.

[A] Glycine and Serine are <u>essential for muscle stem cell production</u> in injured muscles or aged muscles (Leucine shall now fade into obscurity). Also, a diet deficient in these important aminos causes intramuscular lipid accumulation.

"<>Objective: Skeletal muscle regeneration relies on muscle-specific adult stem cells (MuSCs), MuSC progeny, muscle progenitor cells (MPCs), and a coordinated myogenic program that is influenced by the extracellular environment. Following injury, MPCs undergo a transient and rapid period of population expansion, which is necessary to repair damaged myofibers and restore muscle homeostasis. Certain pathologies (e.g., metabolic diseases and muscle dystrophies) and advanced age are associated with dysregulated muscle regeneration. The availability of serine and glycine, two nutritionally non-essential amino acids, is altered in humans with these pathologies, and these amino acids have been shown to influence the proliferative state of non-muscle cells. Our objective was to determine the role of serine/glycine in MuSC/MPC function.
<>Methods: Primary human MPCs (hMPCs) were used for in vitro experiments, and young (4-6 mo) and old (>20 mo) mice were used for in vivo experiments. Serine/glycine availability was manipulated using specially formulated media in vitro or dietary restriction in vivo followed by downstream metabolic and cell proliferation analyses.
<>Results: We identified that serine/glycine are essential for hMPC proliferation. Dietary restriction of serine/glycine in a mouse model of skeletal muscle regeneration lowered the abundance of MuSCs 3 days post-injury. Stable isotope-tracing studies showed that hMPCs rely on extracellular serine/glycine for population expansion because they exhibit a limited capacity for de novo serine/glycine biosynthesis. Restriction of serine/glycine to hMPCs resulted in cell cycle arrest in G0/G1. Extracellular serine/glycine was necessary to support glutathione and global protein synthesis in hMPCs. Using an aged mouse model, we found that reduced serine/glycine availability augmented intermyocellular adipocytes 28 days post-injury.
<>After four weeks of the Ser/Glydepleted diet compared to the control diet, skeletal muscle levels of serine prior to injury decreased by 38% and 42% in the skeletal muscle and plasma, respectively, with a less consistent effect on glycine levels.

<>Strikingly, the aged mice fed the Ser/Gly depleted diet had pronounced intermyocellular adipocyte infiltration, which we confirmed with PERILIPIN-1 staining. The increase in adipocyte infiltration was specific to the injured muscle; there was no significant change in the whole body composition.
<>Conclusions: These studies demonstrated that despite an absolute serine/glycine requirement for MuSC/MPC proliferation, de novo synthesis was inadequate to support these demands, making extracellular serine and glycine conditionally essential for efficient skeletal muscle regeneration."[131.3]

[B] Glycine extends lifespan by reducing Methionine toxicity.

"<>Diets low in methionine extend lifespan of rodents, though through unknown mechanisms. Glycine can mitigate methionine toxicity, and a small prior study has suggested that supplemental glycine could extend lifespan of Fischer 344 rats. We therefore evaluated the effects of an 8% glycine diet on lifespan and pathology of genetically heterogeneous mice in the context of the Interventions Testing Program. Elevated glycine led to a small (4%-6%) but statistically significant lifespan increase, as well as an increase in maximum lifespan, in both males ($p = 0.002$) and females ($p < 0.001$).
<>Pooling across sex, glycine increased lifespan at each of the three independent sites, with significance at $p = 0.01$, 0.053, and 0.03, respectively. Glycine-supplemented females were lighter than controls, but there was no effect on weight in males. End-of-life necropsies suggested that glycine-treated mice were less likely than controls to die of pulmonary adenocarcinoma ($p = 0.03$). Of the 40 varieties of incidental pathology evaluated in these mice, none were increased to a significant degree by the glycine-supplemented diet. In parallel analyses of the same cohort, we found no benefits from TM5441 (an inhibitor of PAI-1, the primary inhibitor of tissue and urokinase plasminogen activators), inulin (a source of soluble fiber), or aspirin at either of two doses.
<>Our glycine results strengthen the idea that modulation of dietary amino acid levels can increase healthy lifespan in mice, and provide a foundation for further investigation of dietary effects on aging and late-life diseases."[131.4]

[C] Serine promotes neural stem cell production following brain injury.

"<>Many experiments have demonstrated that long-term treatment with L-serine increases the levels of neurotrophic factors in the tissue of the injured side of the brain, promoting the proliferation of endogenous NSCs and the repair of neurological function. L-serine regulates microglial polarization, promoting the repair of white matter damage and reducing inflammation. L-serine also reduces neurotoxicity and inhibits the release of inflammatory factors by activating the glycine receptor. In an ischemic brain injury model, L-serine has been found to activate potassium and calcium channels on endothelial cells to increase cerebral blood flow in the ischemic area. As an endogenous amino acid, the safety of L-serine has also been experimentally tested in a phase I human

clinical trial, demonstrating that L-Serine repairs neurological function after secondary injury. The neuroprotective effects of L-serine described herein are so compelling it is tempting to consider how they might translate to humans and obtain satisfactory effects for the clinical use of L-serine. Further studies are also necessary to determine whether, where, and when the levels of L-serine change during disease progression."[131.5]

[D] Glycine promotes mTOR expression, suppresses AMPK, & reduces muscle atrophy factors.

"<>Pro-inflammatory cytokines play a critical role in the pathophysiology of muscle atrophy. We hypothesized that glycine exerted an anti-inflammatory effect and alleviated lipopolysaccharide (LPS)-induced muscle atrophy in piglets. Pigs were assigned to four treatments including the following: 1) nonchallenged control, 2) LPS-challenged control, 3) LPS+1.0% glycine, and 4) LPS+2.0% glycine. After receiving the control, 1.0 or 2.0% glycine-supplemented diets, piglets were treated with either saline or LPS. At 4 h after treatment with saline or LPS, blood and muscle samples were harvested.
<>We found that 1.0 or 2.0% glycine increased protein/DNA ratio, protein content, and RNA/DNA ratio in gastrocnemius or longissimus dorsi (LD) muscles. Glycine also resulted in decreased mRNA expression of muscle atrophy F-box (MAFbx) and muscle RING finger 1 (MuRF1) in gastrocnemius muscle. In addition, glycine restored the phosphorylation of Akt, mammalian target of rapamycin (mTOR), eukaryotic initiation factor 4E binding protein 1 (4E-BP1), and Forkhead Box O 1 (FOXO1) in gastrocnemius or LD muscles. Furthermore, glycine resulted in decreased plasma tumor necrosis factor-α (TNF-α) concentration and muscle TNF-α mRNA abundance.
<>Moreover, glycine resulted in decreased mRNA expresson of Toll-like receptor 4 (TLR4), nucleotide-binding oligomerization domain protein 2 (NOD2), and their respective downstream molecules in gastrocnemius or LD muscles. These results indicate glycine enhances muscle protein mass under an inflammatory condition. The beneficial roles of glycine on the muscle are closely associated with maintaining Akt-mTOR-FOXO1 signaling and suppressing the activation of TLR4 and/or NOD2 signaling pathways."[131.5A]

[E] Glycine activates the AMPA receptors thereby promoting LTP. Unrelated to this book, but an interesting piece of knowledge, the AMPA receptors are prime inducers of seizures in epileptic patients.

"<>Global long-term potentiation (LTP) was induced in organotypic hippocampal slice cultures by a brief application of 10 mM glycine. Glycine-induced LTP was occluded by previous theta burst stimulation-induced potentiation, indicating that both phenomena share similar cellular processes.

<>Glycine-induced LTP was associated with increased [3H]alpha-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) binding in membrane fractions as well as increased amount of a selective spectrin breakdown product generated by calpain-mediated spectrin proteolysis. Antibodies against the C-terminal (C-Ab) and N-terminal (N-Ab) domains of GluR1 subunits were used to evaluate structural changes in AMPA receptor properties resulting from glycine-induced LTP. No quantitative or qualitative changes were observed in Western blots from membrane fractions prepared from glycine-treated slices with C-Ab.
<>In contrast, Western blots stained with N-Ab revealed the formation of a 98-kDa species of GluR1 subunits as well as an increased amount of immunoreactivity after glycine-induced LTP. The amount of spectrin breakdown product was positively correlated with the amount of the 98-kDa species of GluR1 after glycine treatment. Functional modifications of AMPA receptors were evaluated by determining changes in the effect of pressure-applied AMPA on synaptic responses before and after glycine-induced LTP.
<>Glycine treatment produced a significant increase in AMPA receptor function after potentiation that correlated with the degree of potentiation. The results indicate that LTP induction produces calpain activation, truncation of the C-Ab domain of GluR1 subunits of AMPA receptors, and increased AMPA receptor function. They also suggest that insertion of new receptors takes place after LTP induction.[131.5B]

[F] Glycine and Serine concentrations in the brain contribute to mental illness. High levels of Glycine in the Orbitofrontal Cortex, and likely increased AMPAr activity and reduced N-Type Ca(2+) channels (See following study), may contribute to psychoses, mood swings, or impulse control issues in susceptible individuals, whereas low levels of Serine in the Putamen may contribute to depression or apathy.

"<>We have measured the concentrations of glycine and its potential precursors, serine and threonine, in 20 areas of the postmortem brains of chronic schizophrenics and controls using high-performance liquid chromatography by pre-column derivatization with dimethyl-amino-azobenzene sulphonyl chloride. The regional distribution pattern of glycine in the postmortem brains with and without the disease was more similar to that of serine ($r = 0.874$, $P < 0.0001$) than to that of threonine ($r = 0.476$, $P < 0.01$).
<>A multiple regression analysis with regressor variables including diagnosis, age at death and interval between death and freezing revealed that there is a significant difference between schizophrenics and controls in the contents of these amino acids in a number of brain areas. The level of glycine in the orbitofrontal cortex of schizophrenics was found to be significantly increased in schizophrenics, with a tendency to an increase in that of serine. The increase in glycine was also significantly high in the off-drug group of schizophrenics who had not taken antipsychotics more than 40 days before death. Prominent decreases in both glycine and serine were observed in the somesthetic cortex

of the on-drug schizophrenics. Serine was found to be significantly decreased in the putamen of the off-drug schizophrenics. A marked decrease in threonine was also observed in the supramarginal cortex and posterior portion of the lateral occipitotemporal cortex of the off-drug group of schizophrenics and in the putamen of all schizophrenics. <>The highly similar distribution pattern of glycine and serine in the postmortem brains supports the close coupling of synthesis and metabolism between these chemicals in human brains. The increased content of glycine in the orbitofrontal cortex, the reduced level of serine in the putamen and the decrease in threonine in the cerebral cortices, which were prominent in the off-drug schizophrenics, may be involved in the pathophysiology of schizophrenia."[131.5C]

[G] Long term Glycine use causes a reduction in brain N-Type Ca(2+) channels, these channels contribute to neurotransmitter release through activation of Synaptic / Dense Core Vesicles [See: The Brain], making GlySer a supplement that must be cycled frequently to avoid long lasting changes to mood, memory, and personality.

"<>Background: Facilitation of N-methyl-D-aspartate (NMDA) receptor-mediated neurotransmission via administration of glycine site agonists of the NMDA receptor (e.g., glycine, D-serine), and glycine transport inhibitors may represent an innovative pharmacologic strategy in schizophrenia; however, given the potential involvement of NMDA receptors in the neurotoxicity of excitatory amino acids, possible neurotoxic effects of glycinergic compounds need to be explored. Furthermore, studying brain adaptations to chronic administration of glycine site agonists may provide insights into the therapeutic mechanisms of these drugs.
<>Methods: Adult rats were randomized to one of three nutritional regimens (no glycine supplementation, 1 g/kg/day, or 5 g/kg/day glycine supplementation) and to one of three treatment durations (1, 3, or 5 months). Serum glycine and serine levels at sacrifice and brain sections were examined using histologic markers of neurodegeneration (cresyl violet and silver impregnation staining) and immunohistochemical staining of glial fibrillary acidic protein, microtubule-associated protein, and neurofilament 200. To explore additional neural adaptations to high-dose glycine treatment, immunostaining was also performed for class B, N-type Ca(2+) channels.
<>Results: Serum glycine levels increased dose dependently during glycine nutrition, whereas serine levels were not changed. In hippocampal dentate gyrus, the percentage of hypertrophied astrocytes transiently increased at 1 month. At 3 and 5 months of glycine treatment, the density of class B, N-type Ca(2+) channels was reduced in parietal cortex and hippocampus. No evidence of neuronal or glial cell excitotoxic damage or degeneration was registered at either of the treatment intervals studied.
<>Conclusions: These findings demonstrate for the first time that in vivo administration of high-dose glycine may induce brain morphological changes without causing neurotoxic effects. A reduction in density of class B, N-type Ca(2+) channels

in specific brain regions may represent one general adaptation to long-term, high-dose glycine treatment."[131.5D]

[See: Joint Health Supplementation]

As an interjection, I'd like to discuss a term I coin in this book called **Price Of Potency © (POP)**; I intend for it to be used to describe the cost-benefit ratio of supplements. There are many wonderful supplements to be purchased but many are too expensive for their potency. A good example is Astaxanthin which is a superb antioxidant, but in studies it is administered at such a dosage that it would cost hundreds of dollars a month to achieve physiologically beneficial equivalency for a human, and for an average individual that's not monetarily feasible, therefore Astaxanthin has "Extremely High POP" making it a bad supplement.

I have created this simple terminology for classification of supplements by combining a measurement of both efficacy and price to help the reader better understand what supplements offer the best *bang for your buck*.

A supplement with high POP does not mean it is not necessary or outright ineffective, as many chemicals have biological effects that are not easily replicated, and if you have the financial resources, it would be foolish to not invest in your body and brain, but for the average citizen, money is always a stressor, and for these individuals supplementation must be treated as investment, where appreciation is correlated to statistically significant effects.

For those who work harder than they what they earn, it is a wise idea to purchase your supplements one by one, and use them only when a suitable "stack" a compiled.

Anti-Inflammation (AI) (Antioxidant) Cycle Supplementation

"And God said, Behold, I have given you every herb bearing seed, which is upon the face of all the earth, and every tree, in the which is the fruit of a tree yielding seed; to you it shall be for meat."
Genesis: 1:29: Moses

Preface: Multi-Vitamins are toxic, never mix copper or iron with vitamin C or Vitamin A as they will become pro-oxidants (especially ascorbic acid)[1]. Furthermore, vitamin A appears to be the most dangerous vitamin to overdose on due to pro-oxidant effects[2], therefore I have not included it in the Anti-Cycle, as you will likely consume enough with a diet high in leafy green vegetables.

[1] "<>Vitamins with antioxidant properties have the ability to act as pro-oxidants, inducing oxidative damage and oxidative stress as opposed to preventing it. While

vitamin supplements are commonly consumed, the scientific evidence for their health beneficial effects is inconclusive. In fact, even harmful effects have been reported. The present study aimed to investigate and compare pro-oxidant properties of different antioxidants and vitamins commonly found in dietary supplements, at concentrations of physiological relevance, alone or in combination with metals also found in supplements. Focus was on damages related to DNA
<>The vitamins' chemical oxidation potencies were studied by measuring the amount of the oxidation product 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) formed from the DNA nucleoside deoxyguanosine (dG) after vitamin exposure, using a high-performance liquid chromatography system with electrochemical and ultraviolet detection. To study the vitamins' ability to cause DNA damage to cultured cells, promyelocytic leukemia cells (HL-60) were exposed to vitamins, and strand breaks, alkali-labile sites and oxidative DNA lesions, i.e. formamido pyrimidine DNA glycosylase-sensitive sites, were detected using the comet assay. Vitamins A and C chemically induced oxidation of dG, alone and in synergism with iron or copper, whereas only vitamin C and copper induced DNA damage in cultured cells.
<>Contrary, vitamins B1, B2, B3, B6 and B12, β-carotene, folic acid, α-tocopherol, δ-tocopherol or γ-tocopherol did not induce oxidative damage to dG, while lycopene induced a weak dose-response increase. Taken together, vitamin C and copper stood out with the strongest oxidative potency, which is of potential concern since both substances are commonly found in multivitamins.
<>Neither vitamin C nor Cu caused any damage to DNA when added on their own, suggesting that vitamin C and Cu interacted in the cellular system as well. Fe also enhanced the oxidation effect by vitamin C synergistically in the chemical system but not in the cellular."[131.6]

[2] "<>Vitamin A exerts a wide range of physiological roles from embryonic to adulthood stages of the mammalian life. However, there is a great concern regarding the deleterious effects of vitamin A use even therapeutically. It was shown that vitamin A induces behavioral impairments, for instance, anxiety-like behavior and depression, in experimental animals and humans. Caspases are enzymes associated with cell death; however, there is a role for such enzymes also in synaptic plasticity. Then, based on previously published data, we have investigated the effects of vitamin A supplementation at clinical doses (1000-9000 IU/kg/day) for 28 days on caspase-3 and caspase-8 activities in adult rat cerebral cortex, cerebellum, striatum, and hippocampus. Furthermore, we have quantified TNF-alpha levels, a pro-inflammatory cytokine that, besides other biological roles, trigger the extrinsic apoptotic pathway in several cellular types, in those rat brain regions.
<>Interestingly, we found increased caspase-3 activity only in rat cerebral cortex. In all the other regions caspase-3 and caspase-8 activities did not change, as well as the levels of TNF-alpha. The presented results, herein, indicate that more caution is needed regarding vitamin A clinical use and, also importantly, the consumption of vitamin A-fortified foods, which are not exclusively distributed among vitamin A-deficient subjects."[131.7]

Quercetin: Low POP

Quercetin is in my experience the greatest antioxidant on the planet, for it enhances hypertrophy, and promotes bDNF expression, all without severe side-effects.

[A] Quercetin slows myogenesis, halts differentiation, and magnifies hypertrophy. This means if combined with detraining (96h+), Quercetin is anabolic.

"<>While quercetin was shown to accelerate the formation of already existing myotubes (10 > myonuclei) manifested by more numerous large myotubes (increase by 250%) <>Less numerous but larger myotubes found at the end of the experimental period after quercetin could be considered as a sign of higher potency of myoblasts to fuse into existing myotubes- an indirect proof that quercetin might improve hypertrophying muscle."[132]

[B] Quercetin inhibits muscle progenitor cells from transforming into adipocytes.

"In this study, we examined whether quercetin inhibited the adipogenesis of muscle satellite cells in vitro with primary cells from rat limbs by culture in the presence of quercetin under adipogenic conditions. Morphological observations, Oil Red-O staining results, triglyceride content analysis, and quantitative reverse transcription polymerase chain reaction revealed that quercetin was capable of inhibiting the adipogenic induction of muscle satellite cells into adipocytes in a dose-dependent manner by suppressing the transcript levels of adipogenic markers, such as peroxisome proliferator-activated receptor-γ and fatty acid binding protein. Our results suggested that quercetin inhibited the adipogenesis of muscle satellite cells in vitro by suppressing the transcription of adipogenic markers."[133]

[C] Quercetin enhances bDNF.

"<>Quercetin at doses of 20 and 50 mg/kg caused a significant increase in the mRNA expression of BDNF as compared with the control group. Quercetin treatment at a dose of 10 mg/kg failed to cause any significant changes in the levels of BDNF mRNA. <>CONCLUSION: Our findings suggest that the neuroprotective effects of quercetin may be at least partly due to its inducing effects on the expression levels of the BDNF mRNA."[134]

[D] Quercetin reduces amyloid proteins and tau in the brain, making it an absolutely essential supplement for the elderly.

“<>Alzheimer's disease (AD) is the most common senile dementia in the world. Although important progress has been made in understanding the pathogenesis of AD, current therapeutic approaches provide only modest symptomatic relief. In this study, we evaluated the neuroprotective effect of quercetin (25 mg/kg) administration via i.p.

injection every 48 h for 3 months on aged (21-24 months old) triple transgenic AD model (3xTg-AD) mice.
<>Our data show that quercetin decreases extracellular β-amyloidosis, tauopathy, astrogliosis and microgliosis in the hippocampus and the amygdala. These results were supported by a significant reduction in the paired helical filament (PHF), β-amyloid (βA) 1-40 and βA 1-42 levels and a decrease in BACE1-mediated cleavage of APP (into CTFβ). Additionally, quercetin induced improved performance on learning and spatial memory tasks and greater risk assessment behavior based on the elevated plus maze test. Together, these findings suggest that quercetin reverses histological hallmarks of AD and protects cognitive and emotional function in aged 3xTg-AD mice."[134.1]

[E] Quercetin in low dosages is lipolytic and in high dosages adipogenic. I believe the high dose equivalency to humans would be 10g+ per day.

"<>High fat diet (HFD)-induced insulin resistance (IR) is partially characterized by reduced skeletal muscle mitochondrial function and peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC1α) expression. Our previous study showed that a high dose of the bioflavonoid quercetin exacerbated HFD-induced IR; yet, others have demonstrated that quercetin improves insulin sensitivity. The aim of this study was to investigate whether differing doses of quercetin act in a time-dependent manner to attenuate HFD-induced IR in association with improved skeletal muscle mitochondrial function and PGC1α expression.
<>C57BL/6J mice were fed HFD for 3 or 8 wks, with or without a low (50 ug/day; HF+50Q) or high (600 ug/day, HF+600Q) dose of quercetin. Whole body and metabolic phenotypes and insulin sensitivity were assessed. Skeletal muscle metabolomic analysis of acylcarnitines and PGC1α mRNA expression via qRT-PCR were measured.
<>Quercetin at 50 ug/day for 8 wk attenuated HFD-induced increases in fat mass, body weight and IR and increased PGC1α expression, whereas 600 ug/day of quercetin exacerbated fat mass accumulation without altering body weight, IR or PGC1α. PGC1α expression correlated with acylcarnitine levels similarly in HF and HF+600Q; these correlations were not present in HF+50Q. At both time points, energy expenditure increased in HF+50Q and decreased in HF+600Q, independent of PGC1α and IR. Chronic dietary quercetin supplementation at low but not higher dose ameliorates the development of diet-induced IR while increasing PGC1α expression in muscle, suggesting that skeletal muscle may be an important target for the insulin-sensitizing effects of a low dose of quercetin."[135]

[F] Quercetin blocks STAT3.

"<>Evidence has suggested that STAT3 functions as an oncogene in gliomagenesis. As a consequence, changes in the inflammatory microenvironment are thought to promote tumor development. Regardless of its origin, cancer-related inflammation has many tumor-promoting effects, such as the promotion of cell cycle progression, cell proliferation, cell migration and cell survival. Given that IL-6, a major cancer-related

inflammatory cytokine, regulates STAT3 activation and is upregulated in glioblastoma, we sought to investigate the inhibitory effects of the chemopreventive flavonoid quercetin on glioblastoma cell proliferation and migration triggered by IL-6, and to determine the underlying mechanisms of action.
<>In this study, we show that quercetin is a potent inhibitor of the IL-6-induced STAT3 signaling pathway in T98G and U87 glioblastoma cells. Exposure to quercetin resulted in the reduction of GP130, JAK1 and STAT3 activation by IL-6, as well as a marked decrease of the proliferative and migratory properties of glioblastoma cells induced by IL-6. Interestingly, quercetin also modulated the expression of two target genes regulated by STAT3, i.e. cyclin D1 and matrix metalloproteinase-2 (MMP-2). Moreover, quercetin reduced the recruitment of STAT3 at the cyclin D1 promoter and inhibited Rb phosphorylation in the presence of IL-6. Overall, these results provide new insight into the role of quercetin as a blocker of the STAT3 activation pathway stimulated by IL-6, with a potential role in the prevention and treatment of glioblastoma."[136]

Medium Chain Triglyceride Oil (Capric / Caprylic Acid): Moderate POP

Two of the other fatty acids contained within Coconut oil, other than Lauric Acid, sold commonly in formulations created from Palm oil, look instead for Pure Coconut oil extracted MCT oil to avoid Palmitic acid. Remember that one or both of these fatty acids are irritants to the gastrointestinal tract in higher dosages, I'd suggest using no more than two tablespoons per hour, always with food.

MCT oil suppresses TGF-b.

"<>Medium Chain Triglycerides (MCT) is a dietary supplement and usually used along with medications for treating food absorption disorders including diarrhea, steatorrhea and liver disease. It has been shown that MCT plays a role in lowering weight, and decreasing metabolic syndrome, abdominal obesity and inflammation. However, it is still unknown whether MCT enhances exercise endurance. Here, we demonstrated that MCT containing diet improves high temperature induced exercise performance impairment. <>We found that MCT up-regulates the expression and protein levels of genes involved in mitochondrial biogenesis and metabolism. Further investigation demonstrated that the increased mitochondrial biogenesis and metabolism is mediated through the activation of Akt and AMPK signaling pathways and inhibition of TGF-β signaling pathway. Collectively, our findings indicate a beneficial effect of dietary MCT in exercise performance through the increase of mitochondrial biogenesis and metabolism."[136.1]

Silymarin (Milk Thistle Extract): Moderate POP

Silymarin, a group of phytochemicals found in Milk Thistle, stimulates Phosphatase and tensin homolog (PTEN) expression. PTEN depletion promotes enhanced early life myogenesis, but over time causes the exhaustion of the myogenic stem cell pool through increased senescence. Conversely, increasing PTEN activity in muscle tissue will delay

aging-induced deficits in myogenesis. PTEN activity suppresses Insulin signaling via Akt Pathway inhibition, and this may cause hyperglycemia, depending on your body's metabolism and your diet, it is therefore unwise to use large amounts of Silymarin while on a high carbohydrate diet. I predict that every longevity supplement will contain Silymarin after this book is published.
[See: Neurodegeneration: [M]]

[A] Silymarin promotes PTEN expression in Skeletal Muscle. PTEN is the major negative regulator of AKT.

"<>Background and aims: Phosphatase and tensin homolog (PTEN) is a phosphoinositide phosphatase that regulates crucial cellular functions, including insulin signaling, lipid and glucose metabolism, as well as survival and apoptosis. Silymarin is the active ingredient in milk thistle and exerts numerous effects through the activation of PTEN. However, the effect of silymarin on the development of insulin resistance remains unknown.
<>Methods: Wistar rats fed fructose-rich chow or normal chow were administered oral silymarin to identify the development of insulin resistance using the homeostasis model assessment of insulin resistance and hyperinsulinemic- euglycemic clamping. Changes in PTEN expression in skeletal muscle and liver were compared using western blotting analysis. Further investigation was performed in L6 cells to check the expression of PTEN and insulin-related signals. PTEN deletion in L6 cells was achieved by small interfering ribonucleic acid transfection.
<>Results: Oral administration of silymarin at a dose of 200 mg/kg once daily induced insulin resistance in normal rats and enhanced insulin resistance in fructose-rich chow-fed rats. An increase of PTEN expression was observed in the skeletal muscle and liver of rats with insulin resistance. A decrease in the phosphorylation of Akt in L6 myotube cells, which was maintained in a high-glucose condition, was also observed. Treatment with silymarin aggravated high-glucose-induced insulin resistance. Deletion of PTEN in L6 cells reversed silymarin-induced impaired insulin signaling and glucose uptake.
<>Conclusions: Silymarin has the ability to disrupt insulin signaling through increased PTEN expression. Therefore, silymarin should be used carefully in type-2 diabetic patients."[136.2]

[B] PTEN overexpression enhances lifespan through a decrease in cancer incidence, and increased energy expenditure by way of "hyperactive" brown fat & UCP1.

"<>Aging in worms and flies is regulated by the PI3K/Akt/Foxo pathway. Here we extend this paradigm to mammals. Ptentg mice carrying additional genomic copies of Pten are protected from cancer and present a significant extension of life span that is independent of their lower cancer incidence. Interestingly, Ptentg mice have an increased energy expenditure and protection from metabolic pathologies. The brown adipose tissue (BAT) of Ptentg mice is hyperactive and presents high levels of the uncoupling protein Ucp1, which we show is a target of Foxo1. Importantly, a synthetic PI3K inhibitor also

increases energy expenditure and hyperactivates the BAT in mice. These effects can be recapitulated in isolated brown adipocytes and, moreover, implants of Ptentg fibroblasts programmed with Prdm16 and Cebpβ form subcutaneous brown adipose pads more efficiently than wild-type fibroblasts. These observations uncover a role of Pten in promoting energy expenditure, thus decreasing nutrient storage and its associated damage."[136.3]

[C] PTEN ablation causes increased early life muscle hypertrophy followed by satellite cell exhaustion and muscle fibrosis during aging, meaning that increased PTEN expression in muscle tissue throughout life will delay satellite cell senescence. "<>Satellite cell dysfunction leads to failures of muscle repair, but the molecular mechanisms regulating satellite cell homeostasis remain poorly understood. Using conditional knockout approach, our current study demonstrates that loss of Pten in embryonic myoblasts results in postnatal skeletal muscle hypertrophy, better motor function and resistance to denervation-induced muscle atrophy. However, the Pten KO induced muscle hypertrophy is at the expense of disrupting the homeostasis of satellite cells by rendering them at the GAlert state. This transiently promotes early postnatal muscle growth but accelerates satellite cell exhaustion during aging. These findings point to a novel role of Pten in muscle progenitors, and provide functional evidence that prolonged GAlert leads to stem cell depletion and regenerative failure."[136.4]

[See: Neurodegeneration, & Anti-Aging, Lifespan Extension, & Longevity Diets]

Cannabidiol: High POP

Cannabidiol is a very promising chemical, yet it is not easily acquired. "CBD Oils", and "Hemp Extract Oils" contain high concentrations of THC due to the process of decarboxylation, which is an inefficient extraction method, rendering the products neurotoxic. Even supposed *CBD Isolates* have likely had their Cannabidiol concentration degraded to psychotropic Cannabinol through natural room temperature degradation.
The only intelligent way to acquire actual CBD, aside from prescription, is through growing or purchasing immature & extremely fresh, uncured, Trichome-rich Marijuana buds.

As an addendum: For the brainwashed individuals who do not believe their chosen CBD products contain THC, find a manufacturer that lists the batch chemistry results and look closely at the concentration of THC; Even a tenth of a milligram of THC is strongly psychoactive. If you feel dissociated or tired after consuming a dosage of CBD Oil you are experiencing a subtle THC high, nothing more, nothing less.

[A] CBD promotes lifespan.

"<>Introduction: Despite widespread use of cannabidiol (CBD), no lifelong toxicity study has been published to date. Caenorhabditis elegans is often used in preclinical

lifelong toxicity studies, due to an estimated 60-80% of their genes having a human ortholog, and their short lifespan of ~2-3 weeks. In this study, we examined both acute and long-term exposure studies of CBD at physiologically relevant concentrations. <>Materials and Methods: Acute toxicity was determined by treating day 1 adults with a wide range of CBD concentrations (0.4 μM to 4 mM) and assessing mortality and motility compared to control animals. Thermotolerance was examined by treating adult animals with CBD (0.4 μM to 4 mM) and exposing them to 37°C for 4 h, and then scoring for the number of alive animals treated with CBD compared to controls. Long-term toxicity was assessed by exposing day 1 adults to 10, 40, and 100 μM CBD until all animals perished. Control animals had no active drug exposure.
<>Results: We report both acute and long-term exposure studies of CBD to adult C. elegans at physiologically relevant concentrations. Acute toxicity results showed that no animal died when exposed to 0.4-4000 μM CBD. The thermotolerance study showed that 40 μM CBD, but not other treatment levels, significantly increased resistance to heat stress by 141% compared to the untreated controls. Notably, whole-life exposure of C. elegans to 10-100 μM CBD revealed a maximum life extension of 18% observed at 40 μM CBD. In addition, motility analysis of the same groups revealed an increase in late-stage life activity by up to 206% compared to controls. <>Conclusion: These results serve as the only CBD lifelong exposure data in an in vivo model to date. While further research into the lifelong use of CBD should be carried out in mammalian models, the C. elegans model indicates a lack of long-term toxicity at physiologically relevant concentrations."[139.1]

[B] CBD promotes synaptogenesis when used acutely, potentially making this a good supplement to use one day per week, allowing a washout period of six days, for facilitating memory, although using it daily and chronically will most likely yield cognitive benefits, albeit to a lesser degree.

"<>Currently available antidepressants have a substantial time lag to induce therapeutic response and a relatively low efficacy. The development of drugs that addresses these limitations is critical to improving public health. Cannabidiol (CBD), a non-psychotomimetic component of Cannabis sativa, is a promising compound since it shows large-spectrum therapeutic potential in preclinical models and humans. However, its antidepressant properties have not been completely investigated. <>Therefore, the aims of this study were to investigate in male rodents (i) whether CBD could induce rapid and sustained antidepressant-like effects after a single administration and (ii) whether such effects could be related to changes in synaptic proteins/function. Results showed that a single dose of CBD dose-dependently induced antidepressant-like effect (7-30 mg/kg) in Swiss mice submitted to the forced swim test (FST), 30 min (acute) or 7 days (sustained) following treatment. Similar effects were observed in the Flinders Sensitive and Flinders Resistant Line (FSL/FRL) rats and the learned helplessness (LH) paradigm using Wistar rats.
<>The acute antidepressant effects (30 min) were associated with increased expression of synaptophysin and PSD95 in the medial prefrontal cortex (mPFC) and elevated BDNF

levels in both mPFC and hippocampus (HPC). CBD also increased spine density in the mPFC after 30 min, but not 7 days later. Intracerebroventricular injection of the TrkB antagonist, K252a (0.05 nmol/μL), or the mTOR inhibitor, rapamycin (1 nmol/μL), abolished the behavioral effects of CBD. These results indicate that CBD induces fast and sustained antidepressant-like effect in distinct animal models relevant for depression. These effects may be related to rapid changes in synaptic plasticity in the mPFC through activation of the BDNF-TrkB signaling pathway. The data support a promising therapeutic profile for CBD as a new fast-acting antidepressant drug."[139.2]

[C] CBD should be combined with Sesame oil when orally administered to enhance its bioavailability and promote CBD accumulation in important brain regions such as the temporal lobe.

"Studying the temporal lobe, the highest ($p < 0.0001$) Cmax is observed after administration in the sesame oil formulation, at 1979 ± 378 ng/g, where the highest AUC0-t is also seen (4005 ± 1155 h*ng/g). The other three formulations produced similar Cmax and AUCs. The coconut oil formulation appears to show a fall in concentration at 8 h, but this rises again by 12 h post administration. The sesame oil formulation appears to have two smaller concentration peaks at 3 and 8 h, contributing to the highest exposure by this formulation. This is encouraging as the Epidyolex® formulation (a Food and Drug Administration (FDA) approved CBD treatment for seizures associated with rare forms of epilepsy) contains sesame oil, which we demonstrate as a good excipient for improved delivery to the temporal lobe region. There are also high levels of cannabinoid receptors present in the temporal lobe, likely contributing to the high CBD delivery to the region. The delivery profiles of CBD to the parietal lobe appear similar across the formulations studied. All three lipid-based formulations produced higher AUCs than the lipid-free vehicle, and the sesame oil formulation produced a Cmax significantly higher than all other formulations."[139.3]

[D] Cannabidiol inhibits intramuscular ceramide synthesis, who would have thought?

"<>Numerous studies showed that sustained obesity results in accumulation of bioactive lipid derivatives in several tissues, including skeletal muscle, which further contributes to the development of metabolic disturbances and insulin resistance (IR). The latest data indicate that a potential factor regulating lipid and glucose metabolism is a phytocannabinoid—cannabidiol (CBD), a component of medical marijuana (Cannabis). Therefore, we aimed to investigate whether chronic CBD administration influences bioactive lipid content (e.g., ceramide (CER)), as well as glucose metabolism, in the red skeletal muscle (musculus gastrocnemius) with predominant oxidative metabolism. <>All experiments were conducted on an animal model of obesity, i.e., Wistar rats fed a high-fat diet (HFD) or standard rodent chow, and subsequently injected with CBD in a

dose of 10 mg/kg or its solvent for two weeks. The sphingolipid content was assessed using high-performance liquid chromatography (HPLC), while, in order to determine insulin and glucose concentrations, immunoenzymatic and colorimetric methods were used. The protein expression from sphingolipid and insulin signaling pathways, as well as endocannabinoidome components, was evaluated by immunoblotting.
<>Unexpectedly, our experimental model revealed that the significantly intensified intramuscular de novo CER synthesis pathway in the HFD group was attenuated by chronic CBD treatment. Additionally, due to CBD administration, the content of other sphingolipid derivatives, i.e., sphingosine-1-phosphate (S1P) was restored in the high-fat feeding state, which coincided with an improvement in skeletal muscle insulin signal transduction and glycogen recovery."[139.4]

Calcium β-Hydroxy-β-Methyl Butyrate (HMB): Moderate POP

HMB may not be as beneficial for the muscles as for the brain, depending on the amount of leucine consumed in the diet.

[A] HMB promotes neurite outgrowth. [See: Myogenic Regulatory Factors: MEF2]

"<>β-Hydroxy-β-methylbutyrate (HMB) has been shown to enhance cell survival, differentiation and protein turnover in muscle, mainly activating phosphoinositide-3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinases/ extracellular-signal-regulated kinases (MAPK/ERK) signaling pathways. Since these two pathways are related to neuronal survival and differentiation, in this study, we have investigated the neurotrophic effects of HMB in mouse neuroblastoma Neuro2a cells. In Neuro2a cells, HMB promotes differentiation to neurites independent from any effects on proliferation. These effects are mediated by activation of both the PI3K/Akt and the extracellular-signal-regulated kinases (ERK1/2) signaling as demonstrated by the use of specific inhibitors of these two pathways. As myocyte-enhancer factor 2 (MEF2) family of transcription factors are involved in neuronal survival and plasticity, the transcriptional activity and protein levels of MEF2 were also evaluated. HMB promoted MEF2-dependent transcriptional activity mediated by the activation of Akt and ERK1/2 pathways.
<>Furthermore, HMB increases the expression of brain glucose transporters 1 (GLUT1) and 3 (GLUT3), and mTOR phosphorylation, which translates in a higher protein synthesis in Neuro2a cells. Furthermore, Torin1 and rapamycin effects on MEF2 transcriptional activity and HMB-dependent neurite outgrowth support that HMB acts through mTORC2. Together, these findings provide clear evidence to support an important role of HMB in neurite outgrowth."[140.1]

[B] HMB likely promotes myogenic proliferation & prevents muscle atrophy through interacting *weakly* with Histone Deacetylases, similarly to Butyrate or Valproic Acid.

"<>β-Hydroxy-β-Methyl Butyrate (HMB) is a natural catabolite of leucine deemed to play a role in amino acid signaling and the maintenance of lean muscle mass. Accordingly, HMB is used as a dietary supplement by sportsmen and has shown some clinical effectiveness in preventing muscle wasting in cancer and chronic lung disease, as well as in age-dependent sarcopenia. However, the molecular cascades underlying these beneficial effects are largely unknown. HMB bears a significant structural similarity with Butyrate and β-Hydroxybutyrate (βHB), two compounds recognized for important epigenetic and histone-marking activities in multiple cell types including muscle cells. We asked whether similar chromatin-modifying actions could be assigned to HMB as well. Exposure of murine C2C12 myoblasts to millimolar concentrations of HMB led to an increase in global histone acetylation, as monitored by anti-acetylated lysine immunoblotting, while preventing myotube differentiation. In these effects, HMB resembled, although with less potency, the histone deacetylase (HDAC) inhibitor Sodium Butyrate."
"<>However, similar to Butyrate, HMB almost completely prevented terminal differentiation (as monitored by Ckm expression levels) and myotube formation in DM"[140.2]

Rutin: Low POP

An interesting flavonoid structurally related to quercetin.

[A] Rutin reduces muscle atrophy proteins.

"<>One of the causes of sarcopenia is that homeostasis between anabolism and catabolism breaks down due to muscle metabolism changes. Rutin has shown antioxidant and anti-inflammatory effects in various diseases, but there are few studies on the effect on muscle loss with aging. The effect of rutin on muscle loss was evaluated using dexamethasone-induced muscle loss C2C12 myoblast and mouse model.
<>In the group treated with dexamethasone, the muscle weight of gastrocnemius (GA), tibialis anterior (TA), and extensor digitorum longus (EDL) in the mouse model were significantly decreased ($p < 0.0001$ in GA, $p < 0.0001$ in TA, and $p < 0.001$ in EDL) but recovered ($p < 0.01$ in GA, $p < 0.0001$ in TA, and $p < 0.01$ in EDL) when treated with rutin. MAFbx, MuRF1, and FOXO3 protein expression of C2C12 myoblast were significantly increased ($p < 0.01$ in MAFbx, $p < 0.01$ in MuRF1, and $p < 0.01$ in FOXO3) when treated with dexamethasone, but it was recovered ($p < 0.01$ in MAFbx, $p < 0.01$ in MuRF1, and $p < 0.01$ in FOXO3) when rutin was treated. In addition, MAFbx and FOXO3 protein expression in GA of mouse model was significantly increased ($p < 0.0001$ in MAFbx and $p < 0.001$ in FOXO3) when treated with dexamethasone, but it was also recovered ($p < 0.01$ in MAFbx and $p < 0.001$ in FOXO3) when rutin was treated.
<>The present study shows that rutin blocks the FOXO3/MAFbx and FOXO3/MuRf1 pathways to prevent protein catabolism. Therefore, rutin could be a potential agent for

muscle loss such as sarcopenia through the blocking ubiquitin-proteasome pathway associated with catabolic protein degradation."[142]

[B] Rutin (and Quercetin) break down (disaggregate) amyloid fibrils.
"<>Aims: Quercetin and rutin have been reported to exert numerous pharmacological activities, such as free-radical scavenging, effects on immune and inflammatory cell functions, and could have benefits in Alzheimer's disease (AD) by mitigating cellular damage induced by reactive oxygen species (ROS). A key event in AD is the conversion of the β-amyloid (Aβ) peptide into amyloid plaques in the brain. Preventing Aβ aggregation is pursued as a therapeutic strategy for treating AD. In this study, antiamyloidogenic and antioxidant properties of quercetin and rutin were investigated.
<>Main methods: We investigated whether quercetin and rutin affect Aβ25-35 fibrillogenesis, BACE activity and the cellular redox status.
<>Key findings: Quercetin and rutin inhibited the formation of Aβ fibrils and disaggregated Aβ fibrils. β-secretase enzyme (BACE) activity was significantly inhibited by rutin. To resemble the in vivo Aβ-induced neurotoxicity we used a cell system overexpressing APP Swedish mutation (APPswe), which is associated with early-onset familial AD, and may promote oxidative stress due to the enhanced Aβ production. Quercetin and rutin decreased almost completely ROS generation in H(2)O(2)-treated APPswe cells. Both flavonoids increased intracellular GSH content and the redox status, and for rutin this effect was concentration dependent. Besides, quercetin and rutin diminished the index of lipid peroxidation in comparison with control APPswe cells at all concentrations tested.
<>Significance: Our findings may provide an explanation of the neuroprotective effect of quercetin and rutin, suggesting that they could be dietary phytochemicals able to revert the β-amyloid toxicity in vivo."[143]

Aspirin / Salsalate

Aspirin is an acetylated version of a plant defense chemical called Salicylic acid. During metabolism it is converted to Salicylic acid in the body, because it is acetylated it has far greater COX-1 / COX-2 inhibiting properties, this is unlike Salsalate which is another derivative of Salicylic acid, but is not acetylated, leading to less COX-1 / COX-2 inhibition, and greater metabolic but likely not neurological effects. These derivatives of Salicylic acid should not to be considered simply "NSAIDs", they is far more than that, they are metabolized in the body into Salicylic acid, which is an ancient plant defense phytochemical. Salsalate unfortunately requires a prescription, but it is a far better drug to use as a pain reliever as compared to Ibuprofen, Diclofenac, or Acetaminophen.

[A] A low dosage of Aspirin at around 200-400mg promotes hippocampal neurogenesis.

"<>Aspirin has been reported to prevent memory decline in the elderly population. Adult neurogenesis in the hippocampus has been recognized as an underlying basis of learning and memory.

<>This study investigated the effect of aspirin on spatial memory in correlation with the regulation of hippocampal neurogenesis and microglia in the brains of ageing experimental mice. Results from the novel object recognition (NOR) test, Morris water maze (MWM), and cued radial arm maze (cued RAM) revealed that aspirin treatment enhances working memory in experimental mice.
<>Further, the co-immunohistochemical assessments on the brain sections indicated an increased number of doublecortin (DCX)-positive immature neurons and bromodeoxyuridine (BrdU)/neuronal nuclei (NeuN) double-positive newly generated neurons in the hippocampi of mice in the aspirin-treated group compared to the control group. Moreover, a reduced number of ionized calcium-binding adaptor molecule (Iba)-1-positive microglial cells was evident in the hippocampus of aspirin-treated animals. Recently, enhanced activity of acetylcholinesterase (AChE) in circulation has been identified as an indicative biomarker of dementia. The biochemical assessment in the blood of aspirin-treated mice showed decreased activity of AChE in comparison with that of the control group.
<>Results from this study revealed that aspirin facilitates hippocampal neurogenesis which might be linked to enhanced working memory."[143.1]

[B] Aspirin appears to activate CREB through PPARa, leading to improved memory. This effect may be directly related to the acetylated nature of Aspirin, and not shared directly with Salsalate.

"<>Despite its long history, until now, no receptor has been identified for aspirin, one of the most widely used medicines worldwide.
<>Here we report that peroxisome proliferator-activated receptor alpha (PPARα), a nuclear hormone receptor involved in fatty acid metabolism, serves as a receptor of aspirin. Detailed proteomic analyses including cheminformatics, thermal shift assays, and TR-FRET revealed that aspirin, but not other structural homologs, acts as a PPARα ligand through direct binding at the Tyr314 residue of the PPARα ligand-binding domain. On binding to PPARα, aspirin stimulated hippocampal plasticity via transcriptional activation of cAMP response element-binding protein (CREB). <>Finally, hippocampus-dependent behavioral analyses, calcium influx assays in hippocampal slices and quantification of dendritic spines demonstrated that low-dose aspirin treatment improved hippocampal plasticity and memory in FAD5X mice, but not in FAD5X/Ppara-null mice.
<>These findings highlight a property of aspirin: stimulating hippocampal plasticity via direct interaction with PPARα."[143.2]

[C] Salsalate promotes AMPK-B1 expression, but it also unrelatedly promotes mitochondrial uncoupling (proton leakage) in the liver, leading to halted lipogenesis, improved glucose tolerance, and the browning of fat. This means salsalate is an excellent fat burner.

"<>Salsalate is a prodrug of salicylate that lowers blood glucose in patients with type 2 diabetes (T2D) and reduces nonalcoholic fatty liver disease (NAFLD) in animal models;

however, the mechanism mediating these effects is unclear. Salicylate directly activates AMPK via the β1 subunit, but whether salsalate requires AMPK-β1 to improve T2D and NAFLD has not been examined. Therefore, wild-type (WT) and AMPK-β1–knockout (AMPK-β1KO) mice were treated with a salsalate dose resulting in clinically relevant serum salicylate concentrations (~1 mmol/L).
<>Salsalate treatment increased VO2, lowered fasting glucose, improved glucose tolerance, and led to an ~55% reduction in liver lipid content. These effects were observed in both WT and AMPK-β1KO mice.
<>To explain these AMPK-independent effects, we found that salicylate increases oligomycin-insensitive respiration (state 4o) and directly increases mitochondrial proton conductance at clinical concentrations. This uncoupling effect is tightly correlated with the suppression of de novo lipogenesis. Salicylate is also able to stimulate brown adipose tissue respiration independent of uncoupling protein 1. <>These data indicate that the primary mechanism by which salsalate improves glucose homeostasis and NAFLD is via salicylate-driven mitochondrial uncoupling."[143.3]

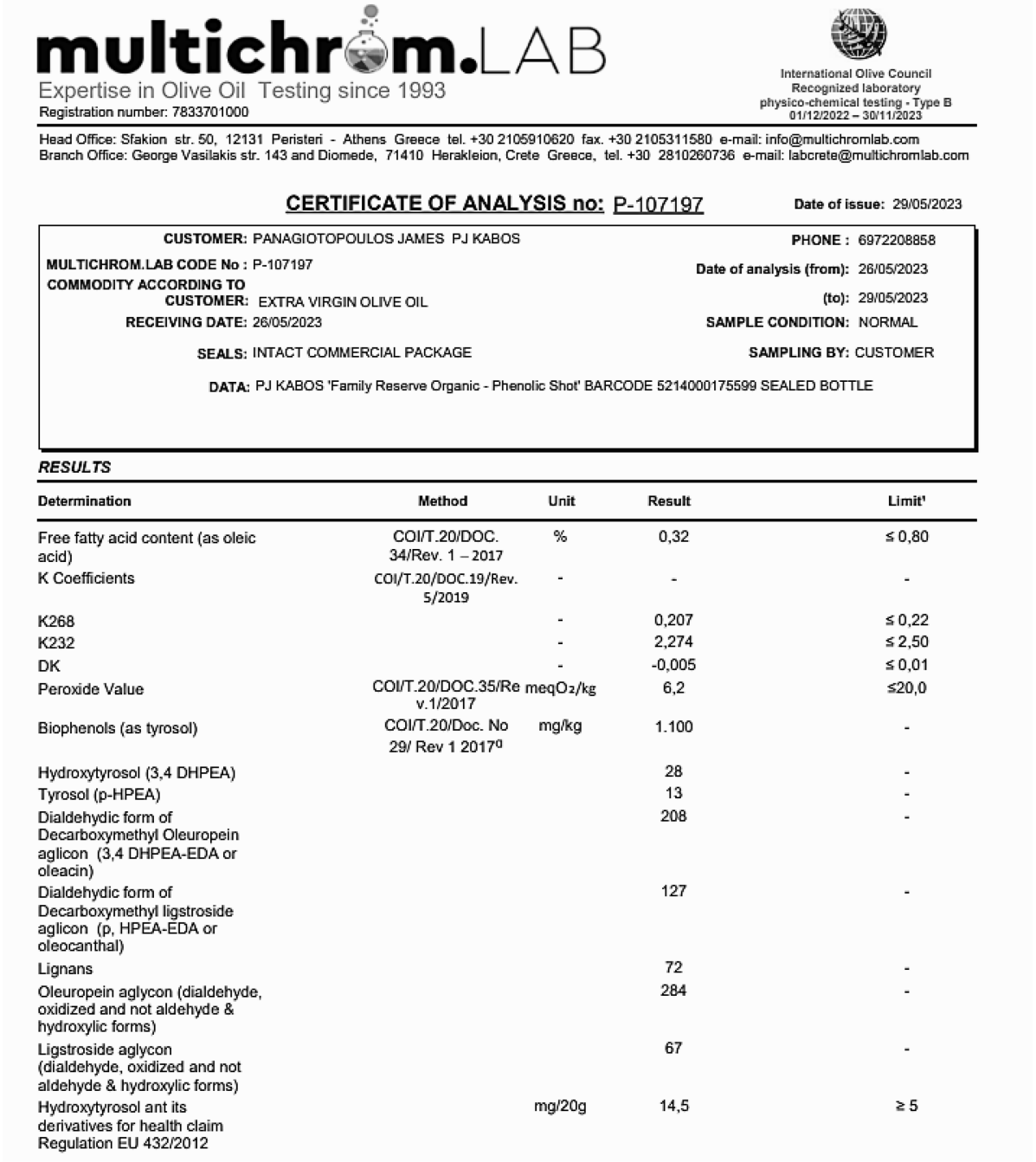
Oleuropein / Hydroxytyrosol: Olive Leaf Extract / Extra Virgin Olive Oil (EVOO)

I am not a fan of traditional olive oils due to their high Oleic acid content, but they contain some notable antioxidants, such as Oleuropein[1] and Hydroxytyrosol[2]. Greek EVOO's contain higher concentrations of these polyphenols then other varieties. Oleuropein can be purchased in encapsulated supplement form, but because Hydroxytyrosol is a breakdown product of Oleuropein that forms during the manufacturing of Olive oil, if you wish to consume adequate amounts of it dietarily the best idea is to combine a concentrated and documented EVOO high in polyphenols (800mg/kg +) such as PJ Kabos Phenolic Shot with another vegetable or seed oil forming a hybrid oil to drizzle on each meal or add to your protein shakes, to reduce your intake of Oleic acid.

The healthiest EVOO's will have a peppery or astringent and unpleasant taste, and if they do not they are clearly devoid of large concentrations of the aforementioned polyphenols. Remember also that when a vegetable oil is exposed to air or UV radiation it will degrade rapidly, you always store your vegetable oils in a cupboard or cabinet. Although I consider Oleic acid to be an unnecessary but forced dietary component, it is not the primary enemy of metabolism or muscle health, that place is held for the dreaded Palmitic Acid. This is why Italians, and Greek individuals have better health indices than Americans, they consume large amounts of Olive oil, whereas we consume large amounts of Palm oil-rich pastries and sweets, one fatty acid promotes the growth of blood vessels, whilst the other inhibits it, one is drizzled on health foods, whilst the other is gratuitously added to junk foods.

For those interested in an overview of the manufacturing process and validity of high polyphenolic EVOO's, here is an HPLC analysis and adetailed explanation courtesy of

James @ PJ Kabos EVOO's regarding the production of his companies polyphenol-rich EVOO "Phenolic Shot" product:



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CERTIFICATE OF ANALYSIS no: P-107197 **Date of issue:** 29/05/2023

CUSTOMER: PANAGIOTOPOULOS JAMES PJ KABOS **PHONE :** 6972208858
MULTICHROM.LAB CODE No : P-107197 **Date of analysis (from):** 26/05/2023
COMMODITY ACCORDING TO CUSTOMER: EXTRA VIRGIN OLIVE OIL **(to):** 29/05/2023
RECEIVING DATE: 26/05/2023 **SAMPLE CONDITION:** NORMAL
SEALS: INTACT COMMERCIAL PACKAGE **SAMPLING BY:** CUSTOMER
DATA: PJ KABOS 'Family Reserve Organic - Phenolic Shot' BARCODE 5214000175599 SEALED BOTTLE

RESULTS

Determination	Method	Unit	Result	Limit'
Free fatty acid content (as oleic acid)	COI/T.20/DOC. 34/Rev. 1 – 2017	%	0,32	≤ 0,80
K Coefficients	COI/T.20/DOC.19/Rev. 5/2019	-	-	-
K268		-	0,207	≤ 0,22
K232		-	2,274	≤ 2,50
DK		-	-0,005	≤ 0,01
Peroxide Value	COI/T.20/DOC.35/Rev.1/2017	meqO_2/kg	6,2	≤20,0
Biophenols (as tyrosol)	COI/T.20/Doc. No 29/ Rev 1 2017[Q]	mg/kg	1.100	-
Hydroxytyrosol (3,4 DHPEA)			28	-
Tyrosol (p-HPEA)			13	-
Dialdehydic form of Decarboxymethyl Oleuropein aglicon (3,4 DHPEA-EDA or oleacin)			208	-
Dialdehydic form of Decarboxymethyl ligstroside aglicon (p, HPEA-EDA or oleocanthal)			127	-
Lignans			72	-
Oleuropein aglycon (dialdehyde, oxidized and not aldehyde & hydroxylic forms)			284	-
Ligstroside aglycon (dialdehyde, oxidized and not aldehyde & hydroxylic forms)			67	-
Hydroxytyrosol ant its derivatives for health claim Regulation EU 432/2012		mg/20g	14,5	≥ 5

"The very high phenolic value is a result of many factors.

- Olives are harvested very early in the season when they are still unripe.
- A specific olive variety, almost exclusive to our area, is used.
- The trees grow on rocky terrain (not sandy).
- The olive trees are not, or minimally, irrigated.
- The trees are located on an incline, so the soil doesn't retain water or humidity.

The last two factors create water stress for the trees, which activates the production of more polyphenols in the olives. It is as if the tree goes into a self-defense mode and produces polyphenols for the olives.

As for the actual oil production, it is definitely a first cold extraction:

- This process should be executed immediately after harvesting the olives (within the shortest time possible) to prevent the olives from going bad, which would release taste defects and increase acidity. Additionally, during early harvest, the ambient temperature is usually higher than later in the season as winter approaches, so the harvested olives deteriorate more quickly.
- Preferably, the extraction is executed in a two-phase olive mill, which uses less water during production compared to a three-phase olive mill.
- The temperature of the olive paste should be on the high end of the extra virgin olive oil production process limits, around (omitted) degrees Celsius. Lower temperatures help the aroma complexity of the product but reduce the phenolic content, while higher temperatures may increase yield but harm quality.

In addition to the above, there are other necessary actions during harvest, production, storage, and bottling to ensure high-phenolic content and overall Extra Virgin Olive Oil quality."

[1] Oleuropein promotes AMPK expression and enhances glucose uptake in skeletal muscle cells.

"<>Aims: Oleuropein has been recognized as an important medicinal compound because of its various biological properties, including anti-cancer, antidiabetic and anti-atherosclerotic activities. Here, we evaluate the antioxidant activity as well as the mechanism of the hypoglycemic effects of oleuropein in C2C12 cells and we establish the mechanism underlying these effects.
<>Main methods: To perform this study, C2C12 cells viability was analyzed via MTT assay and the antioxidant activity was investigated by ROS and TBARS assays. Also, the effect of oleuropein on AMPK and PI3 kinase signaling pathways was evaluated.
<>Key findings: Treatment with oleuropein was able to protect cells against H_2O_2 induced stress in cells. On the other hand, the molecular bases of its actions have been scarcely understood. Oleuropein significantly enhanced glucose consumption and the phosphorylation of AMPK (AMP-activated protein kinase/ACC (acetyl-CoA carboxylase)) and MAPKs (mitogen-activated protein kinases), but not PI3 kinase (Phosphatidylinositol 3-kinase)/Akt. However, the co-treatment of oleuropein and insulin

improved the insulin sensitivity via insulin-dependent (PI3 kinase/Akt) and insulin independent (AMPK/ACC) pathways.
<>These results could be confirmed from the findings of GLUT4 translocation which was strongly enhanced in the case of oleuropein."[144]

[2] Hydroxytyrosol promotes neurogenesis in the aged brain.

"<>The dentate gyrus of the hippocampus is one of two brain areas generating throughout life new neurons, which contribute to the formation of episodic/associative memories. During aging, the production of new neurons decreases, and a cognitive decline occurs. Dietary factors influence neuronal function and synaptic plasticity; among them the phenolic compound hydroxytyrosol (HTyr), present in olive oil, displays neuroprotective effects.
<>As age impacts primarily on the hippocampus-dependent cognitive processes, we wondered whether HTyr could stimulate hippocampal neurogenesis in vivo in adult and aged wild-type mice as well as in the B-cell translocation 1 gene (Btg1) knockout mouse model of accelerated neural aging. We found that treatment with HTyr activates neurogenesis in the dentate gyrus of adult, aged, and Btg1-null mice, by increasing survival of new neurons and decreasing apoptosis. Notably, however, in the aged and Btg1-null dentate gyrus, HTyr treatment also stimulates the proliferation of stem and progenitor cells, whereas in the adult dentate gyrus HTyr lacks any proliferative effect.
<>Moreover, the new neurons generated in aged mice after HTyr treatment are recruited to existing circuits, as shown by the increase of BrdU+ /c-fos+ neurons. Finally, HTyr treatment also reduces the markers of aging lipofuscin and Iba1. Overall, our findings indicate that HTyr treatment counteracts neurogenesis decline during aging."[144.1]

[See: Micro-Essays: The Biomedical Baby: Pg. 948]

Lion's Mane Mushroom Powder: Low POP

Quite interestingly, medicinal mushrooms promote NGF expression in the brain, retina, & spine. Although pure mushroom powders are difficult to find, as most are often laced with brown rice filler, the best source of unadulterated mushroom powders you will find is at Nuts.com. You will know if your Lion's Mane powder is authentic by its harsh astringent taste when consumed in water.

[A] Many medicinal mushrooms enhance NGF.

"<>The positive control (NGF) recorded 26.4 ± 3.6% of neurite-bearing cells. The extraction yield of extracts from the mushrooms are summarised in (omitted). The percentage of neurite bearing cells after treatment with aqueous extracts of G. lucidum (38.4 ± 4.2%), L. rhinocerotis (38.1 ± 2.6%), and ethanol extract of C. militaris (35.8 ± 3.4%) were significantly higher ($p < 0.01$) than NGF control by approximately 1.45-,

1.44- and 1.35-fold, respectively. Aqueous extracts of G. frondosa (33.7 ± 1.5%) and P. giganteus (33.4 ± 4.6%) were also shown to induce significantly ($p < 0.05$) higher neurite bearing cells compared to the NGF control. <>Meanwhile, the aqueous extracts of L. rhinocerotis mycelium, H. erinaceus, G. neo- japonicum, P. pulmonarius, as well as ethanol extracts of H. erinaceus, P. pulmonarius and P. giganteus showed varied neurite outgrowth stimulatory effects with average neurite bearing cells ranging from 26.4 ± 5.4% to 29.6 ± 2.2%. Further, these extracts showed no significant difference when compared to NGF control ($p > 0.05$).
<>Among the plant extracts tested, wolfberry extract did not show any neurite outgrowth activity. The percentage of neurite bearing cells obtained after treatment with 20 μg/ml of ethanol extract of G. biloba (30.3 ± 2.5%) was better than curcumin which gave 26.4 ± 5.4% at 20 μg/ml. The five different mushroom extracts (G. lucidum, L. rhinocerotis, P. giganteus, G. frondosa and C. militaris) each at 20 μg/ml were selected for neurofilament staining."[145]

[B] Medicinal mushrooms enhance NGF *systemically*, with relevance to the spine and eyeballs. This could be of supreme benefit as a CNS-acting ergogenic for powerlifters and combat sports athletes.

"<>Neurodegenerative disease is defined as a deterioration of the nervous system in the intellectual and cognitive capabilities. Statistics show that more than 80-90 million individuals age 65 and above in 2050 may be affected by neurodegenerative conditions like Alzheimer's and Parkinson's disease. Studies have shown that out of 2000 different types of edible and/or medicinal mushrooms, only a few countable mushrooms have been selected until now for neurohealth activity. Hericium erinaceus is one of the well-established medicinal mushrooms for neuronal health. It has been documented for its regenerative capability in peripheral nerve. Another mushroom used as traditional medicine is Lignosus rhinocerotis, which has been used for various illnesses. It has been documented for its neurite outgrowth potential in PC12 cells. <>Based on the regenerative capabilities of both the mushrooms, priority was given to select them for our study. The aim of this study was to investigate the potential of H. erinaceus and L. rhinocerotis to stimulate neurite outgrowth in dissociated cells of brain, spinal cord, and retina from chick embryo when compared to brain derived neurotrophic factor (BDNF). <>Neurite outgrowth activity was confirmed by the immu-nofluorescence method in all tissue samples. Treatment with different concentrations of extracts resulted in neuronal differentiation and neuronal elongation. H. erinaceus extract at 50 μg/mL triggered neurite outgrowth at 20.47%, 22.47%, and 21.70% in brain, spinal cord, and retinal cells. L. rhinocerotis sclerotium extract at 50 μg/mL induced maximum neurite outgrowth of 20.77% and 24.73% in brain and spinal cord, whereas 20.77% of neurite outgrowth was observed in retinal cells at 25 μg/mL, respectively."[146]

[C] NGF enhances muscle satellite cell activity! This leads me to believe that sooner than later we will be able to inject NGF directly into our muscles post-exercise.

"<>Researchers have attempted to use gene- and cell-based therapies to restore dystrophin and alleviate the muscle weakness that results from Duchenne muscular dystrophy (DMD). Our research group has isolated populations of muscle-derived stem cells (MDSCs) from the postnatal skeletal muscle of mice. In comparison with satellite cells, MDSCs display an improved transplantation capacity in dystrophic mdx muscle that we attribute to their ability to undergo long-term proliferation, self-renewal, and multipotent differentiation, including differentiation toward endothelial and neuronal lineages.
<>Here we tested whether the use of nerve growth factor (NGF) improves the transplantation efficiency of MDSCs. We used two methods of in vitro NGF stimulation: retroviral transduction of MDSCs with a CL-NGF vector and direct stimulation of MDSCs with NGF protein. Neither method of NGF treatment changed the marker profile or proliferation behavior of the MDSCs, but direct stimulation with NGF protein significantly reduced the in vitro differentiation ability of the cells. NGF stimulation also significantly enhanced the engraftment efficiency of MDSCs transplanted within the dystrophic muscle of mdx mice, resulting in the regeneration of numerous dystrophin-positive muscle fibers.
vThese findings highlight the importance of NGF as a modulatory molecule, the study of which will broaden our understanding of its biologic role in the regeneration and repair of skeletal muscle by muscle derived cells."[147]

Dehydroepiandrosterone (DHEA): Moderate POP

The primordial hormone that is vital to our brain health, and the safest and most effective nootropic for the elderly, as it is a precursor to testosterone and estrogen. If you are a woman and past the age of Estrogen Replacement Therapy, or a man and unable to pursue Testosterone Replacement Therapy, you should absolutely use this supplement every day.

[A] DHEA enhances PPAR alpha/delta, nuclear receptors essential for lipid metabolism, but also mitochondrial integrity (health), especially neuronal mitochondria.

"<>Dehydroepiandrosterone (DHEA) is a precursor of sex steroid hormones and is converted to testosterone and estradiol. Normally, androgens and estrogens produced adrenal cortex, testis, and ovary; however, recent studies revealed androgens and estrogens are synthesized by peripheral tissues such as brain, skin, liver, kidney, bone, etc. We found skeletal muscles are also capable of synthesizing androgens and estrogens from DHEA. Circulating DHEA provides substrates required for conversion into potent androgens and estrogens in peripheral tissues. Sex steroid hormone administration has important roles: one is that the enhancement of protein synthesis and anabolism, resulting in muscle growth and increased muscle strength. The other is improvement of hyperglycemia through the activation of glucose signaling pathway in skeletal muscle as well as acceleration of muscle lipid metabolism that increase peroxisome proliferator-activated receptor alpha (PPARα) and PPAR delta (PPARδ). We introduce the effect of

DHEA and sex steroid hormones administration on muscle glucose and lipid metabolisms as well as the effect of sex steroid hormone on the muscle hypertrophy."[148]

[B] DHEA enhances bDNF/NGF.

"<>Due to the increasing cases of neurodegenerative diseases in recent years, the eventual goal of nerve repair is very important. One approach for achieving a neuronal cell induction is by regenerative pharmacology. Nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) are neurotrophins that play roles in neuronal development, differentiation, and protection. On the other hand, dehydroepiandrosterone (DHEA) is a neurosteroid which has multiple actions in the nervous system. DHEA could be an important agent in regenerative pharmacology for neuronal differentiation during tissue regeneration. In this study, we investigated the possible role of DHEA to modulate NGF and BDNF production. The in vivo level of neurotrophins expression was demonstrated by ELISA in rat harvested brain cortex. <>Also neurotrophins expression after DHEA treatment was revealed by the increased neurite extension, immunostaining, and BrdU labeling in rats. Anti-NGF and anti-BDNF antibodies were used as suppressive agents on neurogenesis. The results showed that NGF and BDNF are overproduced after DHEA treatment but there is not any overexpression for NT-3 and NT-4. Also DHEA increased neurite extension and neural cell proliferation significantly. Overall, DHEA might induce NGF and BDNF neurotrophins overproduction in cortical neurons which promotes neural cell protection, survival, and proliferation."[149]

Betaine (Trimethylglycine)

Betaine is a byproduct of choline metabolism which has occurred, before synthesis and the availability of supplementation, primarily through choline consumed in the diet. Betaine facilitates the methylation (activation) of processes in our body such as neurotransmitter production, and gene expression.

[A] Betaine enhances myogenic differentiation at the cost of myogenic proliferation and promotes the conversation of fast to slow twitch fibers.

"<>Increasing evidence indicates that muscular dysfunction or alterations in skeletal muscle fiber-type composition not only are involved in muscle metabolism and function but also can limit functional capacity. Therefore, understanding the mechanisms regulating key events during skeletal myogenesis is necessary. Betaine is a naturally occurring component of commonly eaten foods.
<>Here, we showed that 10 mM betaine supplementation in vitro significantly repressed myoblast proliferation and enhanced myoblast differentiation. This effect can be mediated by regulation of miR-29b-3p. Further analysis showed that betaine supplementation in vitro regulated skeletal muscle fiber-type composition through the induction of NFATc1 and the negative regulation of MyoD expression.

<>Furthermore, mice fed with 10 mM betaine in water for 133 days showed no impairment in overall health. Consistently, betaine supplementation increased muscle mass, promoted muscle formation, and modulated the ratio of fiber types in skeletal muscle in vivo. These findings shed light on the diverse biological functions of betaine and indicate that betaine supplementation may lead to new therapies for diseases such as muscular dystrophy or other diseases related to muscle dysfunction. <>KEY MESSAGES: Betaine supplementation inhibits proliferation and promotes differentiation of C2C12 myoblasts. Betaine supplementation regulates fast to slow muscle fiber-type conversion and is associated with NFATc1/MyoD. Betaine supplementation enhances skeletal myogenesis in vivo. Betaine supplementation does not impair health of mice."[150]

[B] Betaine appears to accelerate lipolysis through enhancing mitochondrial biogenesis in fat, and reducing adipogenesis, most importantly resulting in reduced intramuscular fat.

"<>Obesity is a major driver of metabolic diseases such as nonalcoholic fatty liver disease, certain cancers, and insulin resistance. However, there are no effective drugs to treat obesity. Betaine is a nontoxic, chemically stable and naturally occurring molecule. This study shows that dietary betaine supplementation significantly inhibits the white fat production in high-fat diet (HFD)-induced obese mice. This might be due to betaine preventing the formation of new white fat (WAT) and guiding the original WAT to burn through stimulated mitochondrial biogenesis and promoting browning of WAT. <>Furthermore, dietary betaine supplementation decreases intramyocellular lipid accumulation in HFD-induced obese mice. Further analysis shows that betaine supplementation reduced intramyocellular lipid accumulation might be associated with increasing polyunsaturated fatty acids (PUFA), fatty acid oxidation, and the inhibition of fatty acid synthesis in muscle. Notably, by performing insulin-tolerance tests (ITTs) and glucose-tolerance tests (GTTs), dietary betaine supplementation could be observed for improvement of obesity and non-obesity induced insulin resistance. <>Together, these findings could suggest that inhibiting WAT production, intramyocellular lipid accumulation and inflammation, betaine supplementation limits HFD-induced obesity and improves insulin resistance."[150.1]

Hibiscus Sabdariffa: Low POP

[A] Hibiscus Sabdariffa enhances lifespan.

"<>HSE treatment resulted in a prominent extension of lifespan (up to 24%) and a reduction of the age-dependent decline in locomotion. HCA, a main compound of HSE increased lifespan too, but to a lesser extent (6%) while ICA was not effective. HSE and HCA did not modulate resistance against thermal stress conditions and did not exert antioxidative effects: HSE rather increased intracellular ROS levels, suggesting a pro-oxidative effect of the extract in vivo. HSE and HCA increased the nuclear localization of the pivotal transcription factors DAF-16 and SKN-1 indicating an activation of these

factors. Consistent with this result, lifespan prolongation by HSE was dependent on both transcription factors. In addition to the positive effect on lifespan, HSE treatment also elicited a (strong) protection against amyloid-ß induced toxicity in C. elegans in a DAF-16- and SKN-1-dependent manner."[151]

[B] Hibiscus Sabdariffa reduces IL-1B thereby preventing overtraining-induced memory impairments.

"<>Overtraining leads to an increase in IL-1β systemically due to muscle microtrauma, which affects the hippocampus, an important structure in spatial memory consolidation. The administration of Hibiscus sabdariffa Linn is expected to decrease IL-1β and increase IL-1ra, thereby potentially preventing impairments in spatial memory consolidation. This research was an experimental study using 20 male Wistar rats. The overtraining of Wistar rats altered the ratio of IL-1β/IL-1ra in the plasma and hippocampus. Moreover, this overtraining impaired spatial memory consolidation. The methanol extract of H. sabdariffa improved spatial memory consolidation in Wistar rats and prevented impairment in spatial memory consolidation by maintaining the ratio of IL-1β/IL-1ra in the plasma and hippocampus of Wistar rats who experienced overtraining. H. sabdariffa is a potent anti-inflammatory substance that prevents impairments in spatial memory consolidation in overtrained Wistar rats."[152]

Creatine Monohydrate: Low POP

Creatine is in my opinion a far better nootropic than myogenic supplement,

considering it activates the GABAA receptors, and also the fact that its anabolic effects are perturbed through high fat consumption.

[A] Creatine enhances the MRF's Myogenin and most importantly MRF4.

"<>When combined with heavy resistance training, Cr supplementation increases M-CK mRNA expression, likely due to concomitant increases in the expression of myogenin and MRF-4. Therefore, increases in myogenin and MRF-4 mRNA and protein may play a role in increasing myosin heavy chain expression, already shown to occur with Cr supplementation."[153]

[B] Repeated for Effect: MRF4 is essential for muscle force production (neuromuscular junctions).

"<>MRF4 belongs to the basic helix-loop-helix class of transcription factors and this and other members of its family profoundly influence skeletal muscle development. Less is known about the role of these factors in aging. As MRF4 is preferentially expressed in subsynaptic nuclei, we postulated it might play a role in maintenance of the neuromuscular junction. To test this hypothesis, we examined the junctional regions of

19-20-month-old mice and found decreased levels of SV2B, a marker of synaptic vesicles, in MRF4-null mice relative to controls. There was a corresponding decrease in grip strength in MRF4-null mice. Taken together, these data suggest that the intrinsic muscle factor, MRF4 plays an important role in maintenance of neuromuscular junctions."[154]

[C] Creatine has no effect when paired with a high fat diet. Now what does “high fat diet” mean in terms of animal studies? Likely it means a diet high in Palmitic acid & Oleic acid coming from cocoa butter[431.9], with other non-essential fatty acids, but I am not certain how the pairing of Linoleic acid or Alpha Linoleic Acid with Creatine would affects it’s purported anabolic signaling.

"<>High-fat (HF) diets in combination with sedentary lifestyle represent one of the major public health concerns predisposing to obesity and diabetes leading to skeletal muscle atrophy, decreased fiber diameter and muscle mass with accumulation of fat tissue resulting in loss of muscle strength. One strategy to overcome the maleficent effects of HF diet is resistance training, a strategy used to improve muscle mass, reverting the negative effects on obesity-related changes in skeletal muscle. Together with resistance training, supplementation with creatine monohydrate (CrM) in the diet has been used to improve muscle mass and strength. Creatine is a non-essential amino acid that is directly involved in the cross-bridge cycle providing a phosphate group to ADP during the initiation of muscle contraction.
<>Besides its antioxidant and anti-inflammatory effects CrM also upregulates IGF-1 resulting in hyperthophy with an increase in muscle function. However, it is unknown whether CrM supplementation during resistance training would revert the negative effects of high-fat diet on the muscle performance. During 8 weeks we measured muscle performance to climb a 1.1m and 80° ladder with increasing load on trained rats that had received standard diet or high-fat diet, supplemented or not with CrM. <>We observed that the CrM supplementation up-regulated IGF-1 and phospho-AKT protein levels, suggesting an activation of the IGF1-PI3K-Akt/PKB-mTOR pathway. Moreover, despite the CrM supplementation, HF diet down-regulated several proteins of the IGF1-PI3K-Akt/PKB-mTOR pathway, suggesting that diet lipid content is crucial to maintain or improve muscle function during resistance training.
<>These results suggested the necessity to change the diet prior in order to perceive the benefit of resistance training and CrM supplementation."[155]

[D] Creatine is anti-inflammatory, thereby potentially increasing the risk of injury if used when muscles and tendons are recovering from high intensity exercise sessions.

"<>Forty-eight hours prior to competition there was no difference between groups in the plasma concentrations (pg x ml(-1), mean +/- SEM) of IL-6 (7.08 +/- 0.63), TNFalpha (76.50 +/- 5.60), INF alpha (18.32 +/- 1.20), IL-1 beta (23.42 +/- 5.52), and PGE(2) (39.71 +/- 3.8). Twenty-four and 48 h after competition plasma levels of TNFalpha, INF alpha, IL-1 beta and PGE(2) were significantly increased ($P < 0.05$) in both groups.

However, the increases in these were markedly reduced following creatine supplementation. An increase in plasma IL-6 was observed only after 24 h and, in this case, there was no difference between the two groups."[156]

[E] Creatine is a GABAA receptor agonist, meaning it promotes motor learning, thus making its use as a Pre-workout supplement beneficial for mental performance, and describing its addictive anxiolytic mechanism of action.

[F1] "<>The involvement of brain creatine in the adaptation to acute stress responses was investigated in chicks. In experiment 1, brain creatine content of chicks exposed to social separation stress was significantly increased compared with control chicks. The effects of i.c.v. injection of creatine (2 mug) on vocalizations, spontaneous activity and plasma corticosterone concentration in chicks under social separation stress were investigated in experiment 2. All measurements were attenuated by the i.c.v. injection of creatine compared with the controls under separation stress. Creatine also significantly decreased the active posture, but increased the motionless eye-opened posture, compared with the control.
<>To clarify the relationship between creatine function and GABA receptors, the i.c.v. co-injection of creatine with picrotoxin, a GABA-A receptor antagonist, or CGP54626, a GABA-B receptor antagonist, was investigated in experiments 3 and 4. The effects of creatine on vocalizations and spontaneous activity were attenuated by co-injection of picrotoxin. In this case, active postures decreased by creatine were recovered by co-injection with picrotoxin. However, these effects were not obtained with CGP54626. The results suggest that central creatine functions within the CNS to attenuate the acute stress response by acting through GABA-A receptors in chicks."[157]

[F2] "<>The finding that the responsiveness of the GABA system to modulation has a strong relationship with motor learning is suggestive of a possible relevance of GABA in an LTP-like synaptic plasticity in human motor learning. In addition, it offers a strong rationale for the use of interventions, such as anodal tDCS, that decrease GABA in a localized region in conjunction with rehabilitation in the context of stroke, in line with recent findings in an animal model."[158]

[G] Creatine enhances hyperplasia.

"<>In myogenic C(2)C(12) cells, 5 mM creatine increased the incorporation of labeled [(35)S]methionine into sarcoplasmic (+20%, $P < 0.05$) and myofibrillar proteins (+50%, $P < 0.01$). Creatine also promoted the fusion of myoblasts assessed by an increased number of nuclei incorporated within myotubes (+40%, $P < 0.001$). Expression of myosin heavy chain type II (+1,300%, $P < 0.001$), troponin T (+65%, $P < 0.01$), and titin (+40%, $P < 0.05$) was enhanced by creatine. Mannitol, taurine, and beta-alanine did not mimic the effect of creatine, ruling out an osmolarity-dependent mechanism. The addition of rapamycin, the inhibitor of mammalian target of rapamycin/70-kDa ribosomal S6 protein kinase (mTOR/p70(s6k)) pathway, and SB 202190, the inhibitor of p38, completely

blocked differentiation in control cells, and creatine did not reverse this inhibition, suggesting that the mTOR/p70(s6k) and p38 pathways could be potentially involved in the effect induced by creatine on differentiation.
<>Creatine upregulated phosphorylation of protein kinase B (Akt/PKB; +60%, $P < 0.001$), glycogen synthase kinase-3 (+70%, $P < 0.001$), and p70(s6k) (+50%, $P < 0.001$). Creatine also affected the phosphorylation state of p38 (-50% at 24 h and +70% at 96 h, $P < 0.05$) as well as the nuclear content of its downstream targets myocyte enhancer factor-2 (-55% at 48 h and +170% at 96 h, $P < 0.05$) and MyoD (+60%, $P < 0.01$). In conclusion, this study points out the involvement of the p38 and the Akt/PKB-p70(s6k) pathways in the enhanced differentiation induced by creatine in C(2)C(12) cells."[160]

[H] Creatine worsens asthma and may even cause it.

"<>Creatine (Cr) is a substrate for adenosine triphosphate synthesis, and it is the most used dietary supplement among professional and recreative athletes and sportsmen. Creatine supplementation may increase allergic airway response, but the cellular and molecular mechanisms are unknown. We used murine model of OVA-induced chronic asthma and showed that Cr supplementation increased total proteins, ATP level, lymphocytes, macrophages, and IL-5 levels in BALF, as well as IL-5 in the supernatant of re-stimulated mediastinal lymph nodes. IL-5 and IL-13 expression by epithelial cells and by peribronchial leukocytes were increased by Cr. Cr augmented the expression of P2 × 7 receptor by peribronchial leukocytes and by epithelial cells, and increased the accumulation of eosinophils in peribronchial space and of collagen fibers in airway wall. <>In human cells, while Cr induced a release of ATP, IL-6, and IL-8 from BEAS-2B cells, whole blood cells, such as eosinophils, and CD4+ T cells, P2 × 7 receptor inhibitor (A740003) reduced such effects, as denoted by reduced levels of ATP, IL-6, and IL-8. Therefore, Cr supplementation worsened asthma pathology due to activation of airway epithelial cells and peribronchial leukocytes, involving purinergic signaling."[161]

[I] Creatine enhances CD8 T cell activity, which might explain the increase in satellite cell activity following muscle injury.

"<>T cells demand massive energy to combat cancer; however, the metabolic regulators controlling antitumor T cell immunity have just begun to be unveiled. When studying nutrient usage of tumor-infiltrating immune cells in mice, we detected a sharp increase of the expression of a CrT (Slc6a8) gene, which encodes a surface transporter controlling the uptake of creatine into a cell. Using CrT knockout mice, we showed that creatine uptake deficiency severely impaired antitumor T cell immunity. Supplementing creatine to WT mice significantly suppressed tumor growth in multiple mouse tumor models, and the combination of creatine supplementation with a PD-1/PD-L1 blockade treatment showed synergistic tumor suppression efficacy. We further demonstrated that creatine acts as a "molecular battery" conserving bioenergy to power T cell activities. Therefore, our results have identified creatine as an important metabolic regulator controlling

antitumor T cell immunity, underscoring the potential of creatine supplementation to improve T cell–based cancer immunotherapies.
<>"Next, to study how creatine uptake regulates CD8 T cell response to antigen stimulation, we isolated CD8 T cells from CrT-WT or CrT-KO littermate mice, followed by stimulating these cells in vitro with anti-CD3. A standard T cell culture medium was used, which comprised 10% FBS as the source of creatine. After stimulation, WT CD8 T cells showed up-regulated expression of CrT mRNA and CrT protein, indicating the induction of CrT expression by TCR signaling and suggesting, in turn, the need for activated CD8 T cells to uptake more creatine. Compared with their CrT-WT counterparts, CrT-KO CD8 T cells showed a reduction in almost all aspects of T cell activation."[162]

[J] Creatine causes Insulin resistance after *eight weeks of use*, one should then cycle its use on a month-month basis to avoid derangements to health.

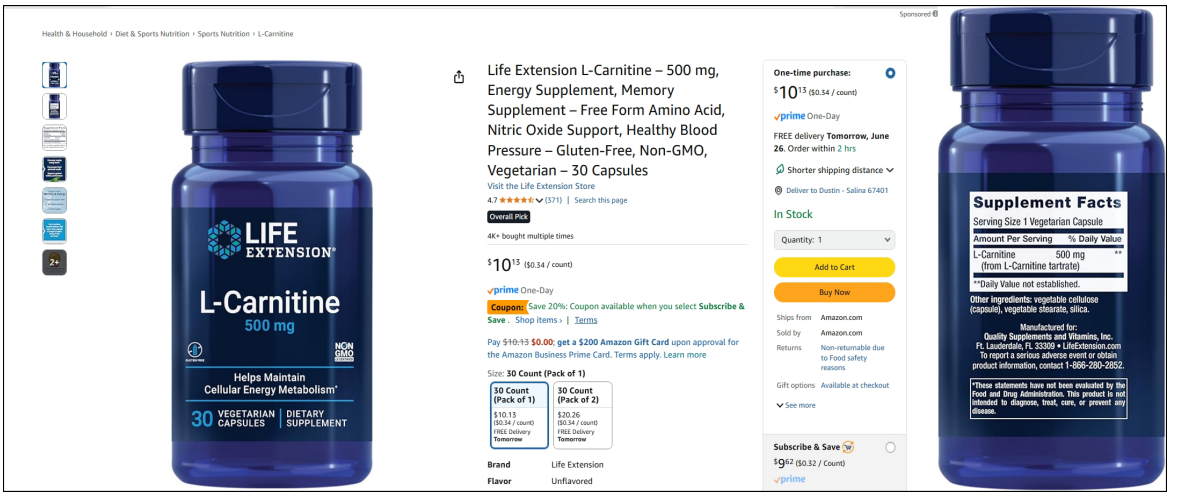
"<>Dietary creatine supplementation has been used to improve skeletal muscle performance. However, dietary creatine manipulation also affects glucose homeostasis. The aim of this study was to investigate the effect of dietary creatine supplementation on insulin secretion, glucose tolerance, and quadriceps glycogen metabolism in chow-fed rats. Forty-eight rats in total were divided into 2 groups of 24 and were then subdivided into 6 groups of 8.
<>Rats were fed a diet supplemented with 0% (CON) or 2% (CREAT) creatine for 2, 4, or 8 weeks. At these 3 time points an oral glucose tolerance test was performed. Two days later, rats were euthanized and the pancreas and quadriceps muscles were collected. The peak insulin response to a glucose challenge was significantly elevated after both 4 (CON 327 +/- 72 v CREAT 735 +/- 140 pmol/L, P =.01) and 8 (CON 248 +/- 48 v CREAT 588 +/- 136 pmol/L, P =.02) weeks. Fasting insulin levels were also increased by creatine supplementation for 8 weeks (CON 78 +/- 14 v CREAT 139 +/- 14 pmol/L, P =.01).
<>Glucose tolerance was not affected until 8 weeks at which point the peak plasma glucose was elevated in the creatine supplemented group (CON 10.1 +/- 0.6 v CREAT 13.5 +/- 1.5 mmol/L, P =.05). A significant increase in pancreatic total creatine content was seen in supplemented animals at 2 (CON 1.2 +/- 0.1 v CREAT 2.7 +/- 0.1 micromol/g wet wt, P =.005), 4 (CON 1.5 +/- 0.2 v CREAT 2.7 +/- 0.3 micromol/g wet wt, P =.02) and 8 (CON 1.5 +/- 0.1 v CREAT 2.6 +/- 0.1 micromol/g wet wt, P =.005) weeks, whereas no change in quadriceps total creatine or glycogen content was observed at any individual time point.
<>This study shows that prolonged creatine supplementation induces abnormalities in pancreatic insulin secretion and changes in glucose homeostasis."[163.1]

L-Carnitine: High POP

L-Carnitine is not equal to Acetylcarnitine, although they may share similar effects on the body, only L-Carnitine can transit into the mitochondria, and it is therefore a far better

antioxidant. Just because a molecule is methylated or acetylated does not make it stronger, or more effective. Unfortunately, the only choice for L-Carnitine supplementation presently is L-Carnitine L-Tartrate. Because Tartaric Acid is a relatively unresearched chemical compound, and it may inhibit myogenesis, angiogenesis, or perturb neuronal function due to its effects on Ca2+, I am against its use. When the time comes where truly Free Form L-Carnitine (not Acetyl-based or Tartrate bounded) reappears on the market, this will be good news, but for the time being we may be forced to use L-Carnitine L-Tartrate, although I would suggest using it sparingly until more research becomes available or better options appear on the market.

As a bonus, I must criticize the supplement company Life Extension who is falsely advertising *Free Form* L-Carnitine, as evidenced by the picture below of their 2025 product titling, Free Form is Free Base, and this means *unbounded*, they are therefore not to be trusted.


Health & Household › Diet & Sports Nutrition › Sports Nutrition › L-Carnitine
LIFE EXTENSION
L-Carnitine
500 mg
Helps Maintain Cellular Energy Metabolism*
30 VEGETARIAN CAPSULES | DIETARY SUPPLEMENT
Life Extension L-Carnitine – 500 mg, Energy Supplement, Memory Supplement – Free Form Amino Acid, Nitric Oxide Support, Healthy Blood Pressure – Gluten-Free, Non-GMO, Vegetarian – 30 Capsules
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Supplement Facts
Serving Size 1 Vegetarian Capsule
Amount Per Serving % Daily Value
L-Carnitine 500 mg ** (from L-Carnitine tartrate)
**Daily Value not established.
Other ingredients: vegetable cellulose (capsule), vegetable stearate, silica.
Manufactured for: Quality Supplements and Vitamins, Inc. Ft. Lauderdale, FL 33309 • LifeExtension.com
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*These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

[A] Very interestingly, Carnitine accelerates complete myogenesis.

"<>The targeting of nutraceutical treatment to skeletal muscle damage is an emerging area of research, driven by the need for new therapies for a range of muscle-associated diseases. L-Carnitine (CARN) is an essential nutrient and plays a key role in mitochondrial β-oxidation and in the ubiquitin-proteasome system regulation. As a dietary supplement to improve athletic performance, CARN has been studied for its potential to enhance β-oxidation. However, CARN effects on myogenesis, mitochondrial activity, and hypertrophy process are not completely elucidated. This in vitro study aims to investigate CARN role on skeletal muscle remodeling, differentiation process, and myotubes formation.
<>We analyzed muscle differentiation and morphological features in C2C12 myoblasts exposed to 5 mM CARN. Our results showed that CARN was able to accelerate C2C12 myotubes formation and induce morphological changes, characterizing the start of

hypertrophy process. In addition, CARN improved AKT activation and downstream cellular signaling pathways involved in skeletal muscle atrophy process prevention. Also, CARN positively regulated the pathways involved in oxidative stress defense. In this work, we provide an interesting novel mechanism of the potential therapeutic use of CARN to treat pathological conditions characterized by skeletal muscle morphological and functional impairment, oxidative stress production, and atrophy process in aging."[166]

[B] Carnitine counteracts caffeine-induced neurotoxicity. An interesting study that both displays Carnitines potent antioxidant effects on brain cells, and also the fact that Caffeine is paradoxically neurotoxic, even if it protects brain cells from amyloid proteins.

"<>This study was conducted to evaluate the protective effect of LC against caffeine-induced cytotoxicity in SH-SY5Y neuroblastoma cell line. Materials and methods: SH-SY5Y neuroblastoma cells were incubated with cytotoxic doses of caffeine (5 and 10 mM) in the presence or absence of LC (1 and 5 mM) for duration of 18-24 h. The antioxidant factors, DNA fragmentation and cytotoxic markers were assessed in treated cells.
<>Results: Our results showed that 5 mM LC for 18 h protected SH-SY5Y cells against cytotoxicity induced by both doses of caffeine. This protection was related to the inhibition of reactive oxygen species generation, the increase in the superoxide dismutase and catalase activities and glutathione content and the prevention of lipid peroxidation in cultured SH-SY5Y cells. Apoptosis markers such as DNA fragmentation and caspase-3 activity were also inhibited by 5 mM LC in caffeine-treated cells.
<>Discussion and conclusion: Our results suggest that LC could protect SH-SY5Y cells from caffeine-induced injury through the inhibition of oxidative damage, mitochondria dysfunction and inhibition of cell apoptosis. Our results indicate that LC therapy may be a valuable approach for the suppression of oxidative stress-related apoptosis in various neural diseases."[167]

[C] L-Tartrate inhibits Ca2+ (Calcium) ion channels, thereby *potentially* suppressing myogenesis or neurogenesis.

"<>In hypertensive rats, oral administration of tartaric acid (.1, .5, 1, 5, and 10 mg/kg) for 2 weeks resulted in 65 ± 7.3 mmHg MAP at 10 mg/kg. This antihypertensive effect was comparable to the orally administered verapamil (10 mg/kg) for 2 weeks which caused a decrease in MAP 60.4 ± 3.8 mmHg. Tartaric acid relaxed phenylephrine (PE) and High K+-induced contractions with EC50 values of .157 (.043-.2) and 1.93 (.07-2) µg/mL in vitro.
<>This endothelium-dependent relaxation was inhibited with atropine (1 µM) and L-NAME (10 µM) pretreatment. Tartaric acid also suppressed phenylephrine contractions in Ca+2 free/EGTA medium and on voltage-dependent calcium channels, causing the concentration–response curves toward right. Tartaric acid induced negative inotropic and

chronotropic effects with EC50 values of .26 (.14-.4) and .60 (.2-.8) in rat atria. It showed its effect by complete blockade against atropine and partially in propranolol pretreatment. <>These findings provide scientific basis to low-dose tartaric acid as an antihypertensive and vasodilatory remedy through muscarinic receptor-linked nitric oxide (NO) pathway and Ca+2 channel antagonist."[167.0]

[See: The Ketogenic Diet: [H] (L-Carnitine)]

Wild Blueberries: Moderate POP

This fruit alongside Chokeberries (Redundant Quercetin-rich fruit) are the most beneficial fruits in my opinion that grow on earth, with the only species of Blueberries that hold pharmacodynamical value being the wild variety (**Vaccinium Angustifolium**) due to their high antioxidant content. Wyman's brand is the best available source of Wild Blueberries I have found in the grocery store (Kroger). When paired with AGE Inhibitors such as Quercetin, or Ascorbic acid, I see no risk in their consumption.

[A] Blueberries enhance bDNF.

"<>Rationale: Flavonoid-rich foods have been shown to be able to reverse age-related cognitive deficits in memory and learning in both animals and humans. However, to date, there have been only a limited number of studies investigating the effects of flavonoid-rich foods on cognition in young/healthy animals.
<>Objectives: The aim of this study was to investigate the effects of a blueberry-rich diet in young animals using a spatial working memory paradigm, the delayed non-match task, using an eight-arm radial maze. Furthermore, the mechanisms underlying such behavioural effects were investigated.
<>Results: We show that a 7-week supplementation with a blueberry diet (2 % w/w) improves the spatial memory performance of young rats (2 months old). Blueberry-fed animals also exhibited a faster rate of learning compared to those on the control diet. These behavioural outputs were accompanied by the activation of extracellular signal-related kinase (ERK1/2), increases in total cAMP-response element-binding protein (CREB) and elevated levels of pro- and mature brain-derived neurotrophic factor (BDNF) in the hippocampus. Changes in hippocampal CREB correlated well with memory performance. Further regional analysis of BDNF gene expression in the hippocampus revealed a specific increase in BDNF mRNA in the dentate gyrus and CA1 areas of hippocampi of blueberry-fed animals.
<>Conclusions: The present study suggests that consumption of flavonoid-rich blueberries has a positive impact on spatial learning performance in young healthy animals, and these improvements are linked to the activation of ERK-CREB-BDNF pathway in the hippocampus."[167.1]

[B] Blueberries reduce adiposity and promote lean mass growth.

"<>Metabolic syndrome can precede the development of type 2 diabetes and cardiovascular disease and includes phenotypes such as obesity, systemic inflammation, insulin resistance, and hyperlipidemia. A recent epidemiological study indicated that blueberry intake reduced cardiovascular mortality in humans, but the possible genetic mechanisms of this effect are unknown. Blueberries are a rich source of anthocyanins, and anthocyanins can alter the activity of peroxisome proliferator-activated receptors (PPARs), which affect energy substrate metabolism.
<>The effect of blueberry intake was assessed in obesity-prone rats. Zucker Fatty and Zucker Lean rats were fed a higher-fat diet (45% of kcal) or a lower-fat diet (10% of kcal) containing 2% (wt/wt) freeze-dried whole highbush blueberry powder or added sugars to match macronutrient and calorie content. In Zucker Fatty rats fed a high-fat diet, the addition of blueberry reduced triglycerides, fasting insulin, homeostasis model index of insulin resistance, and glucose area under the curve. Blueberry intake also reduced abdominal fat mass, increased adipose and skeletal muscle PPAR activity, and affected PPAR transcripts involved in fat oxidation and glucose uptake/oxidation. In Zucker Fatty rats fed a low-fat diet, the addition of blueberry also significantly reduced liver weight, body weight, and total fat mass.
<>Finally, Zucker Lean rats fed blueberry had higher body weight and reduced triglycerides, but all other measures were unaffected. In conclusion, whole blueberry intake reduced phenotypes of metabolic syndrome in obesity-prone rats and affected PPAR gene transcripts in adipose and muscle tissue involved in fat and glucose metabolism."[167.2]

Epigallocatechin Gallate (EGCg): Low POP

[A] EGCg promotes hyperplasia, although this research is conflicting considering EGCg suppresses angiogenesis, and therefore may inhibit terminal differentiation.

"<>Muscle loss is a typical process of aging. Green tea consumption is known to slow down the progress of aging. Their underlying mechanisms, however, remain largely unknown. In this study, we investigated the effect of (-)-epigallocatechin-3-gallate (EGCG), a polyphenolic compound of green tea, on myogenic differentiation and found that EGCG significantly increases myogenic differentiation. After EGCG treatment, the expression of myogenic marker genes, such as myosin heavy chain, are increased through activation of TAZ, a transcriptional coactivator with a PDZ-binding motif. TAZ-knockdown does not stimulate EGCG-induced myogenic differentiation.
<>EGCG facilitates the interaction between TAZ and MyoD, which stimulates MyoD-mediated gene transcription. EGCG induces nuclear localization of TAZ through the dephosphorylation of TAZ at its Ser89 residue, which relieves 14-3-3 binding in the cytosol. Interestingly, inactivation of Lats kinase is observed after EGCG treatment,

which is responsible for the production of dephosphorylated TAZ. Together, these results suggest that EGCG induces myogenic differentiation through TAZ, suggesting that TAZ plays an important role in EGCG induced muscle regeneration."[168]

[B] EGCg protects against fast twitch fiber atrophy, most likely through being a CB1r agonist.

"<>Aging exacerbates muscle loss and slows the recovery of muscle mass and function after disuse. In this study we investigated the potential that epigallocatechin gallate (EGCg), an abundant catechin in green tea, would reduce signaling for apoptosis and promote skeletal muscle recovery in the fast plantaris muscle and the slow soleus muscle after hindlimb unloading (HLS) in senescent animals. Fischer 344 × Brown Norway inbred rats (age 34 mo.) received either EGCg (50 mg/kg body weight), or water daily by gavage. One group of animals received HLS for 14 days and a second group of rats received 14 days of HLS, then the HLS was removed and they recovered from this forced disuse for 2 weeks.
<>Animals that received EGCg over the HLS followed by 14 days of recovery, had a 14% greater plantaris muscle weight (p <0.05) as compared to the animals treated with the vehicle over this same period. Plantaris fiber area was greater after recovery in EGCg (2715.2 ± 113.8 μm^2) vs. vehicle treated animals (1953.0 ± 41.9 μm^2). In addition, activation of myogenic progenitor cells was improved with EGCg over vehicle treatment (7.5% vs. 6.2%) in the recovery animals. Compared to vehicle treatment, the apoptotic index was lower (0.24% vs. 0.52%), and the abundance of pro-apoptotic proteins Bax (−22%), and FADD (−77%) were lower in EGCg treated plantaris muscles after recovery.
<>While EGCg did not prevent unloading-induced atrophy, it improved muscle recovery after the atrophic stimulus in fast plantaris muscles. However, this effect was muscle specific because EGCg had no major impact in reversing HLS-induced atrophy in the slow soleus muscle of old rats."[169]

[C] EGCg promotes neurogenesis.

"<>Adult hippocampal neurogenesis is a lifelong feature of brain plasticity that appears to be critically involved in adult brain function and neurological disease. Recent studies suggest that (-)-epigallocatechin-3-gallate (EGCG), which is the main polyphenolic constituent of green tea, may be used for the prevention and treatment of various neurodegenerative diseases. We hypothesized that EGCG promotes adult neurogenesis, which may be beneficial to hippocampus-dependent learning and memory. We show that EGCG treatment significantly increased the number of 5-bromo-2'-deoxyuridine (BrdU)-labeled cells in adult hippocampal neural progenitor cell (NPC) cultures and in the dentate gyrus of adult mice.
<>Meanwhile, EGCG markedly improved spatial cognition in mice. These events are associated with the sonic hedgehog (Shh) signaling pathway. We observed that EGCG triggered a robust upregulation of Shh receptor (Patched) mRNA and protein expression

in cultured NPCs as well as an upregulation of the downstream Shh transcriptional target Gli1. These changes were further confirmed in the hippocampus of mice administered EGCG. The blockage of the Shh signal with the pharmacological inhibitor cyclopamine attenuated EGCG-induced hippocampal neurogenesis. Our results provide strong evidence that EGCG enhances adult hippocampal neurogenesis."[170]

[D] EGCg is significantly rendered inert by the pairing of it with food, especially amino acids. Always consume it on an empty stomach 60-90min before eating.

"<>The bioavailability of the most abundant and most active green tea antioxidant, epigallocatechin gallate (EGCG) remains uncertain. Therefore, the systemic absorption of EGCG was tested in healthy fasted humans. It was administered as capsules with water or with a light breakfast, or when incorporated within a strawberry sorbet. The results for plasma EGCG clearly revealed that taking EGCG capsules without food was better; the AUC was 2.7 and 3.9 times higher than when EGCG capsules were taken with a light breakfast ($p = 0.044$) or with EGCG imbedded in the strawberry sorbet ($p = 0.019$), respectively. This pattern was also observed for Cmax and Cav.
<>Therefore, ingesting food at the same time as EGCG, whether it was imbedded or not in food, substantially inhibited the absorption of the catechin. As with some types of medications that are affected by food, it appears that EGCG should be taken without food in order to maximise its systemic absorption. Therefore, based on these findings, ingesting EGCG with water on an empty stomach is the most appropriate method for the oral delivery of EGCG in clinical trials where EGCG is to be investigated as a potential bioactive nutraceutical in humans."[171]

[E] EGCg through reducing AMPK / PGC-1a reduces oxidative fiber growth.

"<>Epigallocatechin gallate (EGCG) is a major active compound in green tea polyphenols. EGCG acts as an antioxidant to prevent the cell damage caused by free radicals and their derivatives. In skeletal muscle, exercise causes the accumulation of intracellular reactive oxygen species (ROS) and promotes the formation of slow-type muscle fiber. To determine whether EGCG, as a ROS scavenger, has any effect on skeletal muscle fiber type, we applied different concentrations (0, 5, 25, and 50 μM) of EGCG in the culture medium of differentiated C2C12 cells for 2 days. The fiber-type composition, mitochondrial biogenesis-related gene expression, antioxidant and glucose metabolism enzyme activity, and ROS levels in C2C12 cells were then detected.
<>According to our results, 5 μM EGCG significantly decreased the cellular activity of SDH, 25 μM EGCG significantly downregulated the MyHC I, PGC-1α, NRF-1, and p-AMPK levels and SDH activity while enhancing the CAT and GSH-Px activity and decreasing the intracellular ROS levels, and 50 μM EGCG significantly downregulated MyHC I, PGC-1α, and NRF-1 expression and HK and SDH activity while increasing LDH activity.
<>Furthermore, 300 μM H_2O_2 and 0.5 mM AMPK agonist (AICAR) improved the expression of MyHC I, PGC-1α, and p-AMPK, which were all reversed by 25 μM

EGCG. In conclusion, the effect of EGCG on C2C12 cells may occur through the reduction of the ROS level, thereby decreasing both AMPK activity and PGC-1α expression and eventually reducing slow-twitch muscle fiber formation and mitochondrial biosynthesis."[172]

[I] EGCg blocks STAT3.

"<>Signal transducer and activator of transcription 3 (STAT3) is an oncogene that promotes cell survival, proliferation, and motility. In the present study, we explored the mechanism involved in the inhibition by epigallocatechin-3-gallate (EGCG) of STAT3 signaling as detected by surface plasmon resonance (SPR)-binding assays and in silico docking. Stat3-binding assay indicated that EGCG significantly interrupted Stat3 peptide binding at micromolar concentrations, and the docking experiments indicated that EGCG had a strong interaction with Arg-609, one of the key residues in the STAT3 SH2 domain that contributes greatly to Stat3 and phosphorylated peptide binding.
<>Following treatment of the hepatocellular carcinoma cell lines BEL-7402 and QGY-7703 with EGCG, in vitro, EGCG significantly suppressed cell proliferation as detected by MTT assay, induced apoptosis as detected by flow cytometry, dramatically lowered the expression levels of phosphorylated Stat3 proteins (p-Stat3) as determined by immunoblot detection, and inhibited the expression of multiple genes including Bcl-xL, c-Myc, VEGF and cyclin D1 as demonstrated by RT-PCR analysis.
<>In conclusion, our research data indicate that the anticancer function of green tea results from the inhibition of the STAT3 signaling pathway by EGCG."[173]

[J] EGCg reduces Dopamine availability in the brain, which may lead to negative mood changes.

"<>Dopamine transporter (DAT) provides not only an integral component of dopaminergic neurotransmission but also a molecular gateway for the accumulation of some neurotoxins such as 1-methyl-4-phenylpyridinium (MPP(+)), a metabolite of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP). Previous study reported that the neuroprotective effects of green tea polyphenols against MPP(+)-induced neurotoxicity were related to its inhibitory effect on MPP(+) uptake via DAT in dopaminergic cells.
<>To extend the study, we investigated (-)-epigallocatechin gallate (EGCG), a monomer of green tea polyphenols, on DAT internalization in DAT-overexpressed PC12 cells. We found that EGCG (1-100 microM) can induce a dose-dependent inhibition of dopamine uptake in DAT-PC12 cells. In parallel, treatment of EGCG decreased membrane-bound DAT by 15% to 60%.
<>Furthermore, protein kinase C (PKC) inhibitor GF109203X at 2 microM can markedly diminish the inhibitory effects of EGCG on dopamine uptake and reverse the EGCG-induced internalization of DAT. In addition, semiquantitative RT-PCR analysis indicated that EGCG did not affect DAT mRNA expression in the PC12 cells. These data suggest that EGCG exerts its inhibitory effect on DAT by modulating DAT internalization, in which PKC activation may be involved."[174]

[K] EGCg reduces Tau Protein in the brain.

“Tau aggregation and accumulation is a key event in the pathogenesis of Alzheimer's disease. Inhibition of Tau aggregation is therefore a potential therapeutic strategy to ameliorate the disease. Phytochemicals are being highlighted as potential aggregation inhibitors. Epigallocatechin-3-gallate (EGCG) is an active phytochemical of green tea that has shown its potency against various diseases including aggregation inhibition of repeat Tau. The potency of EGCG in altering the PHF assembly of full-length human Tau has not been fully explored. By various biophysical and biochemical analyses like ThS fluorescence assay, MALDI-TOF analysis and Isothermal Titration Calorimetry, we demonstrate dual effect of EGCG on aggregation inhibition and disassembly of full-length Tau and their binding affinity. The IC50 for Tau aggregation by EGCG was found to be 64.2 μM.”[174.A]

[L] EGCg transforms amyloid fibrils (the precursors to plaques) and alpha-synuclein bundles into non-toxic aggregates.

“<>Protein misfolding and formation of beta-sheet-rich amyloid fibrils or aggregates is related to cellular toxicity and decay in various human disorders including Alzheimer's and Parkinson's disease. Recently, we demonstrated that the polyphenol (-)-epi-gallocatechine gallate (EGCG) inhibits alpha-synuclein and amyloid-beta fibrillogenesis. It associates with natively unfolded polypeptides and promotes the self-assembly of unstructured oligomers of a new type. Whether EGCG disassembles preformed amyloid fibrils, however, remained unclear.
<>Here, we show that EGCG has the ability to convert large, mature alpha-synuclein and amyloid-beta fibrils into smaller, amorphous protein aggregates that are nontoxic to mammalian cells. Mechanistic studies revealed that the compound directly binds to beta-sheet-rich aggregates and mediates the conformational change without their disassembly into monomers or small diffusible oligomers. These findings suggest that EGCG is a potent remodeling agent of mature amyloid fibrils.”[174.B]

[M] EGCg enhances the absorption of dietary mercury.

“<>Fish has many health benefits but is also the most common source of methylmercury. The bioavailability of methylmercury in fish may be affected by other meal components. In this study, the effect of green tea on the bioavailability of methylmercury from an oral bolus of fish muscle tissue was studied in rats and compared to a water treated control group and a group treated with meso-2,3-dimercaptosuccinic acid (DMSA), a compound used medically to chelate mercury. Rats were given a single oral dose of fish tissue via gavage and one of the treatments. Rats were given access to food for 3 h at 12 h intervals. They were dosed with each of the treatments with each meal. Blood samples were collected for 95 hours.

<>Green tea significantly increased the concentration of total mercury in blood relative to the control, whereas DMSA significantly decreased it. In addition, feeding caused a slight increase in blood mercury for several meals following the initial dose."[174.C]

[N] EGCg promotes AMPK expression through ROS, which appear to increase Ca2+ within cells to activate a calcium protein called CaMKK, which activates AMPK production.

"<>Epigallocatechin-3-gallate (EGCG), a main catechin of green tea, has been suggested to inhibit hepatic gluconeogenesis. However, the exact role and related mechanism have not been established. In this study, we examined the role of EGCG in hepatic gluconeogenesis at concentrations that are reachable by ingestion of pure EGCG or green tea, and are not toxic to hepatocytes.
<>Our results show in isolated hepatocytes that EGCG at relatively low concentrations (<or=1 microm) inhibited glucose production via gluconeogenesis and expression of key gluconeogenic genes. EGCG was not toxic at these concentrations while demonstrating significant cytotoxicity at 10 mum and higher concentrations. EGCG at 1 mum or lower concentrations effective in suppressing hepatic gluconeogenesis did not activate the insulin signaling pathway, but activated 5'-AMP-activated protein kinase (AMPK). The EGCG suppression of hepatic gluconeogenesis was prevented by blockade of AMPK activity.
<>In defining the mechanism by which EGCG activates AMPK, we found that the EGCG activation of AMPK was mediated by the Ca(2+)/calmodulin-dependent protein kinase kinase (CaMKK).
<>Furthermore, our results show that the EGCG activation of AMPK and EGCG suppression of hepatic gluconeogenesis were both dependent on production of reactive oxygen species (ROS), which was a known activator of CaMKK.
<>Together, our results demonstrate an inhibitory role for EGCG in hepatic gluconeogenesis and shed new light on the mechanism by which EGCG suppresses gluconeogenesis."[174.D]

Magnesium: Moderate POP

Because of the lack of oral bioavailability and dubious claims of bound forms of Magnesium, the only four forms of Magnesium that are suggested to be used are Magnesium Malate, Magnesium Glycinate, Magnesium Carbonate of which converts to Magnesium Chloride when a chemical reaction with hydrochloric acid occurs in the stomach, and finally Magnesium Chloride Flakes (preferred over magnesium sulphate do sulfate potentially irritating the skin) which when added to a high temperature bath absorbs through the sweat glands at an unknown rate. As Magnesium derivates are the

most commonly used laxatives on the market, it is suggested that you not use oral Magnesium products with other supplements.

[A] Magnesium Carbonate (Chloride) is relatively safe.

"<>MgSO4 is routinely used in therapeutics despite its toxicity. The aim of the present review was to compare MgSO4 and MgCl2 effects in order to answer the question whether MgSO4 could be or not replaced by MgCl2. Considering that the two salts have both similar and proper effects, a clear-cut conclusion is not easy to draw. However, choosing MgCl2 seems advisable because of its more interesting clinical and pharmacological effects and its lower tissue toxicity as compared to MgSO4."[174.1]

[B] Magnesium does absorb into the skin, over extended periods of time.

"<>Therefore, cellular magnesium uptake is only being carried out by specific magnesium transporters and not by diffusion. However, since dead cells of the upper skin layer do not contain functional magnesium transporters, which have not yet been identified in detail, magnesium absorption may be possible only at the small area of sweat glands and hair follicles. A recently published study showed that magnesium ions can penetrate the stratum corneum in a concentration and time dependent manner which is significantly facilitated by hair follicles.
<>However, hair follicles and sweat glands constitute only 0.1% to 1% of the skin surface. Even if a substance is absorbed in this area, the question of the clinical relevance of absorbed amounts needs to be addressed. In the study that examined the permeation of topically applied magnesium no information is given on the quantity of absorbed magnesium"[174.2]

[C] High physiological levels of Magnesium likely promote obesity by reducing brown fat activity.

"<>Aims/hypothesis: Hypomagnesaemia (blood Mg2+ <0.7 mmol/l) is a common phenomenon in individuals with type 2 diabetes. However, it remains unknown how a low blood Mg2+ concentration affects lipid and energy metabolism. Therefore, the importance of Mg2+ in obesity and type 2 diabetes has been largely neglected to date. This study aims to determine the effects of hypomagnesaemia on energy homeostasis and lipid metabolism.
<>Methods: Mice (n = 12/group) were fed either a low-fat diet (LFD) or a high-fat diet (HFD) (10% or 60% of total energy) in combination with a normal- or low-Mg2+ content (0.21% or 0.03% wt/wt) for 17 weeks. Metabolic cages were used to investigate food intake, energy expenditure and respiration. Blood and tissues were taken to study metabolic parameters and mRNA expression profiles, respectively. <>Results: We show that low dietary Mg2+ intake ameliorates HFD-induced obesity in mice (47.00 ± 1.53 g vs 38.62 ± 1.51 g in mice given a normal Mg2+-HFD and low Mg2+-HFD, respectively,

$p < 0.05$). Consequently, fasting serum glucose levels decreased and insulin sensitivity improved in low Mg2+-HFD-fed mice. Moreover, HFD-induced liver steatosis was absent in the low Mg2+ group. In hypomagnesaemic HFD-fed mice, mRNA expression of key lipolysis genes was increased in epididymal white adipose tissue (eWAT), corresponding to reduced lipid storage and high blood lipid levels. Low Mg2+-HFD-fed mice had increased brown adipose tissue (BAT) Ucp1 mRNA expression and a higher body temperature. No difference was observed in energy expenditure between the two HFD groups."
"<>In our study, the reduced WAT mass of LowMg-HFD-fed mice was associated with enhanced lipolysis gene expression, causing high serum NEFA and triacylglycerol levels. These findings suggest that LowMg-HFD-fed mice depend more on mitochondrial β-oxidation, rather than glycolysis, for energy production."[174.3]

[C2] Another study illustrating the adipogenic effect of Magnesium by suppressing brown fat activity.

"<>Aims/hypothesis: Hypomagnesaemia (blood Mg2+ <0.7 mmol/l) is a common phenomenon in individuals with type 2 diabetes. However, it remains unknown how a low blood Mg2+ concentration affects lipid and energy metabolism. Therefore, the importance of Mg2+ in obesity and type 2 diabetes has been largely neglected to date. This study aims to determine the effects of hypomagnesaemia on energy homeostasis and lipid metabolism.
<>Methods: Mice (n = 12/group) were fed either a low-fat diet (LFD) or a high-fat diet (HFD) (10% or 60% of total energy) in combination with a normal- or low-Mg2+ content (0.21% or 0.03% wt/wt) for 17 weeks. Metabolic cages were used to investigate food intake, energy expenditure and respiration. Blood and tissues were taken to study metabolic parameters and mRNA expression profiles, respectively.
Results: We show that low dietary Mg2+ intake ameliorates HFD-induced obesity in mice (47.00 ± 1.53 g vs 38.62 ± 1.51 g in mice given a normal Mg2+-HFD and low Mg2+-HFD, respectively, $p < 0.05$). Consequently, fasting serum glucose levels decreased and insulin sensitivity improved in low Mg2+-HFD-fed mice.
<>Moreover, HFD-induced liver steatosis was absent in the low Mg2+ group. In hypomagnesaemic HFD-fed mice, mRNA expression of key lipolysis genes was increased in epididymal white adipose tissue (eWAT), corresponding to reduced lipid storage and high blood lipid levels. Low Mg2+-HFD-fed mice had increased brown adipose tissue (BAT) Ucp1 mRNA expression and a higher body temperature. No difference was observed in energy expenditure between the two HFD groups.
<>Conclusions/interpretation: Mg2+-deficiency abrogates HFD-induced obesity in mice through enhanced eWAT lipolysis and BAT activity."

[D] L-Malate (in relation to Magnesium L-Malate) when orally administered decreases GABA in the brain, making it an excellent excitatory nootropic at the cost of slightly increased anxiety levels.

"<>Oral administration of L-malate 600 mg.kg-1 for 5 days before training can significantly promote memory acquisition, consolidation and retrieval, respectively, on anisodine-, chloramphenicol-, and ethanol-induced memory impairment in mice. Ketamine (8.5 mg.kg-1, i.p.), a selective NMDA receptor antagonist, was found to inhibit the anti-amnesic activity of L-malate. The glutamate (Glu) and GABA content in mice brain was measured by high-performance liquid chromatography with fluorescence detection. The content of GABA was shown to be decreased from 2.3 +/- 0.5 mumol.g-1 to 1.3 +/- 0.5 mumol.g-1 ($P < 0.01$), so the Glu/GABA ratio was increased significantly. <>These results suggest that the decrease of cerebral GABA level and the increase of Glu/GABA ratio is favorable to learning and memory."[174.4]

[D2] GABAA Receptor inhibition promotes bDNF expression, or more relevantly, reduced GABAA Receptor activity due to decreased GABA in the brain will lead to increased bDNF expression.

"<>Memory consolidation is the process by which acquired information is converted to something concrete to be retrieved later. Here we examined a potential role for brain-derived neurotrophic factor (BDNF) in mediating the enhanced memory consolidation induced by the GABA(A) receptor antagonist, bicuculline methiodide. With the administration of an acquisition trial in naïve mice using a passive avoidance task, mature BDNF (mBDNF) levels were temporally changed in the hippocampal CA1 region, and the lowest levels were observed 9 h after the acquisition trial. In the passive avoidance task, bicuculline methiodide administration within 1 h of training but not after 3 h significantly increased latency time in the retention trial 24 h after the acquisition trial. Concomitantly, 1 h post-training administration of bicuculline methiodide, which enhanced memory consolidation, significantly increased mBDNF levels 9 h after training compared to those of the vehicle-treated control group.
<>In addition, exogenous human recombinant BDNF (hrBDNF) administration 9 h after training into the hippocampal CA1 region facilitated memory consolidation confirming that the increase in mBDNF at around 9 h after training plays a key role in the enhancement of memory consolidation. Moreover, the increases in latency time and immediate early gene expressions by bicuculline methiodide or hrBDNF were significantly blocked by anisomycin, a protein synthesis inhibitor, K252a, a tyrosine receptor kinase (Trk) inhibitor, or anti-TrkB IgG.
<>These findings suggest that the increase in the level of mBDNF and its function during a restricted time window after training are required for the enhancement of memory consolidation by GABA(A) receptor blockade."[174.5]

Iodine: Low POP

Iodine is a vital primordial immunomodulatory compound. Iodine deficiency is simply explained as thyroid hormone deficiency, with thyroid hormone being vital to cognitive function, especially in children.

"<>It is widely accepted that iodine exerts important actions on the immune system. The thymus, as well as many immune cells, have the ability to capture and metabolize iodine. This element can act as an inhibitor or activator of the immune response depending on the cellular context. In cell damage models induced by non-infectious agents it has been shown that iodine prevents the inflammatory response with a radical scavenging effect. It has described that iodine promoted inhibition of ROS production and oxygen consumption of human polymorphonuclear leukocytes, decreased neutrophil chemotaxis and inhibited human complement, mast cell degranulation, nitric oxide and TNF-α production by murine and human macrophages. Iodine is oxidized by myeloperoxidase into free radical iodine and is used to kill bacteria. This ancestral defense mechanism has been documented in Roseolovirus spp. bacteria as a defense against other species. In addition, iodide supplementation increases granulocyte chemotaxis to inflamed areas and improves phagocytosis of bacteria."[175]

Lutein: High POP

[A] Lutein protects skeletal muscle by way of antioxidant mechanisms.

"<>The results showed that Lutein treatment significantly decreased the oxidative stress by reducing reactive oxygen species, protein carbonylation and sulphydryls, lipid peroxidation. Further, the levels of Nrf-2 and antioxidant status was significantly declined during IR injury compared to sham operated rats. Lutein treatment reduced the oxidative stress by enhancing Nrf-2 levels and antioxidant status. Skeletal IR injury enhanced the inflammatory signaling by up regulating NF-κB, COX-2 and various pro-inflammatory cytokines. NF-κB, COX-2 expressions were down regulated by Lutein treatment."[176]

[B] Lutein promotes memory.

"<>Seven studies using MRI (brain activities during rest, cognitive tasks, and brain structure) and two studies using EEG were included. We mainly focused on MRI studies. Three intervention studies using MRI indicated that 10 mg lutein intake over 12 months had a positive impact on healthy older adults' brain activities during learning, resting-state connectivity, and gray matter volumes. Four cross-sectional studies using MRI suggested that lutein was positively associated with brain structure and neural efficiency during cognitive tasks."[177]

Ascorbic Acid: Low POP

[A] Ascorbic acid is myogenic through promoting hyperplasia.

"<>The study demonstrated that AA drives mesoderm-derived stem cell differentiation toward myogenesis and osteogenesis and also inhibits adipogenesis. Further experiments found that AA competes with retinoic acid (RA) to drive cell differentiation in a dose-dependent manner: AA inhibited neurogenic differentiation and stimulated myogenesis whereas RA did the reverse. The AA-dependent differentiation of embryonic stem cells was shown to involve a p38 MAPK/CREB pathway, probably stimulated by cAMP via adenylate cyclases. In addition, SVCT2, the intracellular transporter of AA, acted as a receptor.

<>Finally, we showed that activation/repression of specific differentiation markers is associated with epigenetic changes in their associated promoters. We discuss the impact of these findings in terms of obesity and aging."[178]

[B] Ascorbic acid promotes bDNF.

"<>Oxidative stress and free radical production have been implicated in Alzheimer's disease, where low levels of the antioxidant vitamin C (ascorbate) have been shown to be associated with the disease. In this study, neuroblastoma SH-SY5Y cells were treated with hydrogen peroxide in the presence of ascorbate in order to elucidate the mechanism(s) of protection against oxidative stress afforded by ascorbate. Protein oxidation, glutathione levels, cell viability and the effects on the proteome and its oxidized counterpart were monitored.
<>SH-SY5Y cells treated with ascorbate prior to co-incubation with peroxide showed increased viability in comparison to cells treated with peroxide alone. This dual treatment also caused an increase in protein carbonyl content and a decrease in glutathione levels within the cells. Proteins, extracted from SH-SY5Y cells that were treated with either ascorbate or peroxide alone or with ascorbate prior to peroxide, were separated by two-dimensional gel electrophoresis and analyzed for oxidation. Co-incubation for 24 hours decreased the number of oxidised proteins (e.g. acyl CoA oxidase 3) and induced brain derived neurotrophic factor (BDNF) expression. Enhanced expression of BDNF may contribute to the protective effects of ascorbate against oxidative stress in neuronal cells."[179]

[C] Ascorbic acid (and all antioxidants) reduce lipolysis by suppressing Reactive oxygen species-induced mitochondrial biogenesis (slow twitch fiber oxidative efficiency & growth).

"<>Exercise practitioners often take vitamin C supplements because intense muscular contractile activity can result in oxidative stress, as indicated by altered muscle and blood glutathione concentrations and increases in protein, DNA, and lipid peroxidation. There is, however, considerable debate regarding the beneficial health effects of vitamin C supplementation. This study was designed to study the effect of vitamin C on training

efficiency in rats and in humans. The human study was double-blind and randomized. Fourteen men (27-36 y old) were trained for 8 wk. Five of the men were supplemented daily with an oral dose of 1 g vitamin C. In the animal study, 24 male Wistar rats were exercised under 2 different protocols for 3 and 6 wk. Twelve of the rats were treated with a daily dose of vitamin C (0.24 mg/cm2 body surface area).
<>The administration of vitamin C significantly (P=0.014) hampered endurance capacity. The adverse effects of vitamin C may result from its capacity to reduce the exercise-induced expression of key transcription factors involved in mitochondrial biogenesis. These factors are peroxisome proliferator-activated receptor co-activator 1, nuclear respiratory factor 1, and mitochondrial transcription factor A. Vitamin C also prevented the exercise-induced expression of cytochrome C (a marker of mitochondrial content) and of the antioxidant enzymes superoxide dismutase and glutathione peroxidase. Vitamin C supplementation decreases training efficiency because it prevents some cellular adaptations to exercise."[180]

[D] Ascorbic Acid strangely utilizes oxidative stress to enhance DNA repair.

"<>The hypothesis that vitamin C stimulates DNA repair by temporarily inducing oxidative stress was supported by gene expression analysis. A change in expression of several dozen genes was observed after CCRF-HSB-2 cell exposure to 150 μmol/L vitamin C or ascorbic acid 2-phosphate (AA2P) and incubated up to 24 h. GdC (deoxycytidine glyoxal) levels in culture supernatant are increased after vitamin C treatment which indicates enhanced repair processes—NER removes adducts from DNA. According to genomics analysis AA2P has a higher potential than AA. In the case of AA2P genes involved in the cell cycle, stress response, and DNA repair are induced which does not occur for ascorbate.
<>Expression of following genes relevant to DNA repair is upregulated: *XRCC5* (3.05-fold), *ERCC* (2.49-fold), *RAD18* homologue (2.27-fold), and *RAD50* homologue (2.07-fold). However, the effect is short-lived leading to a positive adaptive response. Other gene expression profiling studies on primary human dermal fibroblasts (GM5659) show the effect of AA and AA2P on DNA repair. The cells were incubated with 100 μM of AA2P, or AA for 5 days (with daily repletion). The expression profiling showed modulation of 294 genes, including those involved in replication, cell cycle regulation, and DNA repair. Expression of Flap structure-specific endonuclease 1 (*FEN1*) and replication factor C (*RFC*) taking part in long-patch BER is enhanced by 2-fold and 2.1-fold, respectively; expression level of one of the glycosylases initiating BER, Nei endonuclease VIII-like 3 (*NEIL3*) increased 2.9-fold; *H2AX,* and *RAD51* which are essential for double strand breaks (DSBs) repair increased 2.1-fold and 2.5-fold, respectively.
<>Induction of this set of genes by ascorbic acid 2-phosphate may help the cell to repair and neutralize the negative effects of oxidative lesions that arise during replication."[180.1]

Vitamin-K as MK-7: Moderate POP

Vitamin K2 MK-4 has greater potency over K1, and Vitamin K2 MK-7 has greater potency over both K1 & MK-4 due to having a longer half-life.

[A] Vitamin K improves mitochondrial biogenesis.

"VK2 supplementation could effectively ameliorate the development of IR by improving mitochondrial function in both HFD-fed mice and palmitate acid-exposed cells. We revealed for the first time that HFD-caused mitochondrial dysfunction could be reversed by VK2 treatment. VK2 enhanced the mitochondrial function by improving mitochondrial respiratory capacity, increasing mitochondrial biogenesis and the enzymatic activities of mitochondrial complexes through SIRT1 signaling. The benefits of VK2 were abrogated in C_2C_{12} transfected with *SIRT1* siRNA but not in C_2C_{12} transfected with *AMPK* siRNA. VK2 and SRT1720, a specific agonist of SIRT1, had the same effect on improving mitochondrial function *via* SIRT1 signaling. Thus, SIRT1 is required for VK2 improvement in skeletal muscle. Further, the beneficial effects of both VK2 and geranylgeraniol contribute to inhibited IR in skeletal muscle *via* SIRT1."[181]

[B] MK-4 (Vitamin K2) promotes muscle hypertrophy (proliferation), another paradoxical antioxidant.

"<>Skeletal muscle function is highly dependent on the ability to regenerate, however, during ageing or disease, the proliferative capacity is reduced, leading to loss of muscle function. We have previously demonstrated the presence of vitamin K2 in bovine skeletal muscles, but whether vitamin K has a role in muscle regulation and function is unknown. In this study, we used primary bovine skeletal muscle cells, cultured in monolayers in vitro, to assess a potential effect of vitamin K2 (MK-4) during myogenesis of muscle cells. Cell viability experiments demonstrate that the amount of ATP produced by the cells was unchanged when MK-4 was added, indicating viable cells. Cytotoxicity analysis show that MK-4 reduced the lactate dehydrogenase (LDH) released into the media, suggesting that MK-4 was beneficial to the muscle cells. Cell migration, proliferation and differentiation was characterized after MK-4 incubation using wound scratch analysis, immunocytochemistry and real-time PCR analysis.
<>Adding MK-4 to the cells led to an increased muscle proliferation, increased gene expression of the myogenic transcription factor myod as well as increased cell migration. In addition, we observed a reduction in the fusion index and relative gene expression of muscle differentiation markers, with fewer complex myotubes formed in MK-4 stimulated cells compared to control cells, indicating that the MK-4 plays a significant role during the early phases of muscle proliferation. Likewise, we see the same pattern for the relative gene expression of collagen 1A, showing increased gene expression in proliferating cells, and reduced expression in differentiating cells. Our results also suggest that MK-4 incubation affect low density lipoprotein receptor-related protein 1

(LRP1) and the low-density lipoprotein receptor (LDLR) with a peak in gene expression after 45 min of MK-4 incubation.
<>Altogether, our experiments show that MK-4 has a positive effect on muscle cell migration and proliferation, which are two important steps during early myogenesis."[182]

[C] "<>MK-7 has higher efficacy due to its higher bioavailability and longer half-life than other vitamin K homologs."[183]

Vitamin-E as Alpha Tocopherol: Low POP

Vitamin E reduces upregulated muscle atrophy factors in unloaded (detrained) muscles, MuRF1 and MAFbx, and even reduces Caspase-3 activity.

"<>Exposure to reduced activity induces skeletal muscle atrophy. Oxidative stress might contribute to muscle wasting via proteolysis activation. This study aimed to test two hypotheses in rats. First, supplementation of the antioxidant vitamin E, prior and during the phase of unloading, would partly counteract unloading-induced soleus muscle atrophy. Secondly, vitamin E supplementation would decrease the rate of muscle proteolysis by reducing expression of calpains, caspases-3, -9, and -12, and E3 ubiquitin ligases (MuRF1 and MAFbx). Soleus muscle atrophy (-49%) induced by 14 days of hindlimb unloading was reduced to only 32% under vitamin E. Vitamin E partly prevented the decrease in type I and IIa fiber size.
<>Supplementation increased HSP72 content and suppressed the rise in muscle level of thiobarbituric acid-reactive substance caused by unloading but failed to modify the lower ratio of reduced vs oxidized glutathione, the higher uncoupling proteins mRNA, and the antioxidant enzyme activities (superoxide dismutase, catalase, and glutathione peroxidase) observed after unloading. Vitamin E treatment abolished the large upregulation of caspases-9 and -12 and MuRF1 transcripts in unloaded muscle and greatly decreased the upregulation of mu-calpain, caspase-3, and MAFbx mRNA. <>In conclusion, the protective effect of vitamin E might be due to modulation of muscle proteolysis-related genes rather than to its antioxidant function."[184]

Beta-Alanine: Low POP

This superb amino acid, which enhances muscle Carnosine concentrations, should be incorporated into both cycles (an angiogenic Pro-Inflmmation Cycle, not an IL-6 Pro-Inflammation Cycle), but be aware it is vital that if you plan on using Beta-Alanine, you use low daily dosages of Taurine, preferably Pre or Intra-Workout, as *chronic Beta-Alanine concentrations in the body will cause Taurine depletion*, thereby resulting in potential retinal damage, and permanent vision loss[184.1].
Furthermore, Beta-Alanine appears to cause a reduction in Histidine concentrations, therefore they should always be paired. Beta-Alanine also reduces IL-6[184.2] but may promote angiogenesis through enhanced intramuscular Carnosine stores.

[A] Beta-Alanine is immunomodulatory through T/B-Cell activation.

"<>Physiological factors involved in immunity and tissue repair with regulate homeostasis, a physiological function of the connective tissue, are as yet unidentified. We earlier detected the granulation-promoting action of carnosine, and reported on the acceleration of tissue repair in experimental as well as clinical studies. In that study, immunoregulatory effects of carnosine and beta-alanine were examined by the plaque-forming cell (PFC) count and delayed hypersensitivity reaction (DHR). The PFC value increased in mice pretreated with these agents. In these mice, PFC reaction to 2 X 10(7) SRBC was enhanced but that to 1 X 10 SRBC was suppressed. The agents also suppressed excess immunoreaction in immature mice but increased weakened immunoreaction in aged animals. Furthermore, the agents had the optimal doses for the enhancement of both PFC reaction to 1 X 10 SRBC and DHR to 1% picryl chloride. <>They also induced recovery of immunofunction suppressed by the administration of MMC. Carnosine and beta-alanine exerts immunoregulatory effects by activating both T and B cells. Our observations indicated that the agents not only promote tissue repair but also help maintain homeostasis and accelerate spontaneous healing."[185]

[B] Beta-Alanine increases MEF-2, which is of interest towards counteracting Creatine-induced MRF4 upregulation.

"β-alanine-treated myotubes displayed significantly elevated markers of improved oxidative metabolism including elevated peroxisome proliferator-activated receptor β/δ (PPARβ/δ) and mitochondrial transcription factor a (TFAM) which led to increased mitochondrial content (evidenced by concurrent increases in cytochrome c content). Additionally, β-alanine-treated cells exhibited significantly increased oxygen consumption compared to control in a PPARβ/δ-dependent manner. β-alanine significantly enhanced expression of myocyte enhancer factor 2 (MEF-2) leading to increased glucose transporter 4 (GLUT4) content."[186]

[C] Beta-Alanine enhances muscle contractility.

“<>Carnosine (beta-alanyl-l-histidine) is present in high concentrations in human skeletal muscle. The ingestion of beta-alanine, the rate-limiting precursor of carnosine, has been shown to elevate the muscle carnosine content. We aimed to investigate, using proton magnetic resonance spectroscopy (proton MRS), whether oral supplementation with beta-alanine during 4 wk would elevate the calf muscle carnosine content and affect exercise performance in 400-m sprint-trained competitive athletes.
<>Fifteen male athletes participated in a placebo-controlled, double-blind study and were supplemented orally for 4 wk with either 4.8 g/day beta-alanine or placebo. Muscle carnosine concentration was quantified in soleus and gastrocnemius by proton MRS. Performance was evaluated by isokinetic testing during five bouts of 30 maximal voluntary knee extensions, by endurance during isometric contraction at 45% maximal voluntary contraction, and by the indoor 400-m running time.

<>beta-Alanine supplementation significantly increased the carnosine content in both the soleus (+47%) and gastrocnemius (+37%). In placebo, carnosine remained stable in soleus, while a small and significant increase of +16% occurred in gastrocnemius. Dynamic knee extension torque during the fourth and fifth bout was significantly improved with beta-alanine but not with placebo. Isometric endurance and 400-m race time were not affected by treatment.
<>In conclusion, 1) proton MRS can be used to noninvasively quantify human muscle carnosine content; 2) muscle carnosine is increased by oral beta-alanine supplementation in sprint-trained athletes; 3) carnosine loading slightly but significantly attenuated fatigue in repeated bouts of exhaustive dynamic contractions; and 4) the increase in muscle carnosine did not improve isometric endurance or 400-m race time."[187]

[D] Beta-Alanine promotes bDNF expression.

"<>The effect of 30 days of β-alanine supplementation (100 mg/kg) on behavioral response and expression of brain-derived neurotrophic factor (BDNF), neuropeptide Y (NPY), and markers of inflammation was examined in both young (4 months) and older (14 months) rats.
<>We hypothesized that animals fed β-alanine would experience reduced inflammation and an enhanced neurotrophin and behavioral response. Animals were assigned to either a control group, in which young or older rats were fed regular chow and water, or a β-alanine group, in which rats were fed regular chow and provided β-alanine in their water. Behavior measures were conducted following the 30-day supplementation period, which included spatial learning, memory, and an anxiety index. Hippocampal expressions of BDNF, NPY, glial fibrillary acidic protein, nuclear factor-κB p50 and p65 subunits, tumor necrosis factor-α, and cyclooxygenase-2 were also analyzed. Learning ability was reduced ($P = .001$) and anxiety index was higher ($P = .001$) in older compared to young rats. Similarly, BDNF and NPY expressions were reduced and all inflammatory markers were elevated ($P < .05$) in the older animals.
<>β-Alanine increased BDNF expressions in the cornu ammonis area 1 ($P = .003$) and 3 ($P < .001$) subregions of the hippocampus. BDNF expression for younger rats in the β-alanine group was also significantly greater than younger rats in the control group in cornu ammonis area 3. Learning for young animals fed β-alanine was significantly better than all other groups. Significant reductions in anxiety were noted in both older and younger rats fed β-alanine compared to age-matched controls. Results indicated that β-alanine ingestion in both young and older rats was effective in attenuating anxiety and augmenting BDNF expression in the hippocampus."[187.1]

[E] Beta-Alanine reduces cellular Histidine concentrations, making it necessary to combine them during supplementation.

"<>Purpose: Carnosine is a dipeptide composed of β-alanine and L-histidine and is present in skeletal muscle. Chronic oral β-alanine supplementation can induce muscle carnosine loading and is therefore seen as the rate-limiting factor for carnosine synthesis.

However, the effect of L-histidine supplementation on carnosine levels in humans is never established. This study aims to investigate whether 1) L-histidine supplementation can induce muscle carnosine loading and 2) combined supplementation of both amino acids is more efficient than β-alanine supplementation alone.
<>Methods: Fifteen male and 15 female participants were equally divided in three groups. Each group was supplemented with either pure β-alanine (BA) (6 g·d), L-histidine (HIS) (3.5 g·d), or both amino acids (BA + HIS). Before (D0), after 12 d (D12), and after 23 d (D23) of supplementation, carnosine content was evaluated in soleus and gastrocnemius medialis muscles by H-MRS, and venous blood samples were collected. Muscle biopsies were taken at D0 and D23 from the vastus lateralis. Plasma and muscle metabolites (β-alanine, histidine, and carnosine) were measured by high-performance liquid chromatography.
<>Results: Both BA and BA + HIS groups showed increased carnosine concentrations in all investigated muscles, with no difference between these groups. By contrast, carnosine levels in the HIS group remained unaltered. Histidine levels were significantly decreased in plasma (-30.6%) and muscle (-31.6%) of the BA group, and this was prevented when β-alanine and L-histidine were supplemented simultaneously.
<>Conclusion: We confirm that β-alanine, and not L-histidine, is the rate-limiting precursor for carnosine synthesis in human skeletal muscle. Yet, although L-histidine is not rate limiting, its availability is not unlimited and gradually declines upon chronic β-alanine supplementation. The significance of this decline still needs to be determined, but may affect physiological processes such as protein synthesis."[187.2]

[F] Beta-Alanine appears to enhance lymphocyte activity thereby accelerating wound regeneration, but it may magnify aging associated immunosenescence. Although I do not believe Beta-Alanine will negatively affect aged muscle tissue considering its Acrolein-binding abilities (read on).

"<>Physiological factors involved in immunity and tissue repair with regulate homeostasis, a physiological function of the connective tissue, are as yet unidentified. We earlier detected the granulation-promoting action of carnosine, and reported on the acceleration of tissue repair in experimental as well as clinical studies. In that study, immunoregulatory effects of carnosine and beta-alanine were examined by the plaque-forming cell (PFC) count and delayed hypersensitivity reaction (DHR). The PFC value increased in mice pretreated with these agents.
<>In these mice, PFC reaction to 2 X 10(7) SRBC was enhanced but that to 1 X 10(9) SRBC was suppressed. The agents also suppressed excess immunoreaction in immature mice but increased weakened immunoreaction in aged animals. <>Furthermore, the agents had the optimal doses for the enhancement of both PFC reaction to 1 X 10(8) SRBC and DHR to 1% picryl chloride. They also induced recovery of immunofunction suppressed by the administration of MMC. Carnosine and beta-alanine exerts immunoregulatory effects by activating both T and B cells. Our observations indicated that the agents not only promote tissue repair but also help maintain homeostasis and accelerate spontaneous healing."[187.3]

[G] Beta-Alanine, like Creatine, is best *cycled*, as its beneficial effects on muscle performance dissipate after four weeks.

"<>Hill and coworkers examined the effects of four and ten weeks of β-ALA supplementation on muscle carnosine concentration and high-intensity cycling capacity. They also sought to discover whether the effects were muscle type specific. Physically active males supplemented with either β-ALA or maltodextrin as a placebo. β-ALA was given in eight doses per day with increasing dose amounts during the first four weeks ranging from 250-750 mg per dose. Subjects underwent muscle biopsies and maximal cycle performance tests at various points during the study.
<>The group supplementing with β-ALA had significantly greater muscle carnosine concentrations at four and ten weeks from 19.9 ± 1.9 to 30.1 ± 2.3 (30.4%) and 34.7 ± 3.7 (35.1%) $mmol \cdot kg^{-1}dm$. There was no significant change with placebo. The change between four and ten weeks with β-ALA was not significant despite the small increase ($p \sim 0.07$). The results also indicated no difference between fiber types, in that each showed similar increases in carnosine as measured by HPLC with fluorescence detection.
<>The authors suggested that the possible benefits from β-ALA supplementation may be limited to four weeks, which is in agreement with previous findings by Suzuki and coworkers who showed an increase in the ability to sustain power output after four weeks of supplementation with no additional benefits observed at ten weeks."[187.4]

[H] Intramuscular Carnosine concentrations (and therefore Beta-Alanine supplementation) appear to enhance angiogenesis through the promotion of VEGF expression. Because Carnosine has low bioavailability, Beta-Alanine is a much more effective way to enhance muscle carnosine stores.

"<>Carnosine synthetase (ATPGD1) is an ATP grasp enzyme that catalyzes formation of histidyl dipeptides such as carnosine (β-alanine-histidine) and anserine (β-alanine-methyl histidine). These dipeptides are food constituents found in a high concentration in the skeletal muscle (10-20 mM) that have the abilities to chelate metals, scavenge lipid peroxidation products and buffer intracellular pH. These dipeptides are regarded as protective against injury and stress.
<>Despite this knowledge, whether carnosine regulates angiogenesis is unknown. To assess this potential, a model of hindlimb ischemia (HLI) was surgically induced by femoral artery and vein ligation in the C57BL/6J (wild type, WT) mice provided drinking water without or with carnosine (1g/L) for 21 days post-surgery. C57BL/6J WT mice subjected to HLI and supplemented with carnosine had increased skeletal muscle expression of the dipeptide/histidine transporter (PHT1), carnosine transport, improved blood flow recovery, re-vascularization and regeneration of myocytes in the ischemic limb compared with mice without carnosine. To support that elevated skeletal muscle carnosine was beneficial in HLI, transgenic mice overexpressing ATPGD1 in the skeletal muscle were constructed."
"<>Because faster recovery of blood flow in the carnosine-supplemented mice was accompanied with increased expression of hypoxia inducible factor (HIF-1α) and

vascular endothelial factor (VEGF) in the ischemic limb, we further investigated the mechanistic connection. Skeletal muscle myoblasts C2C12 cells pretreated with octyl-D-carnosine and subjected to 1 h of hypoxia, replacing oxygen with 95% N2 and 5% CO2, had enhanced HIF-1α translocation, VEGF mRNA and secretion compared with untreated hypoxic and normoxic cells.
<>Collectively, our results demonstrate that carnosine improves ischemia-stimulated angiogenesis potentially by stabilizing HIF1-α and promoting VEGF formation suggesting that carnosine may be a useful therapy in critical limb ischemia."[187.5]

Beta-Carotene: Low POP

[A] Beta-Carotene is anabolic through suppressing atrophy factors and promoting the growth of slow twitch fibers.

"<>Supplements and naturally occurring nutraceuticals effective for maintenance or enhancement of skeletal muscle mass are expected to contribute to prevention of decreased mobility and increased risk of developing metabolic diseases. However, information about available food components remains widely unavailable. In the present study, we investigated the effects of dietary β-carotene on the quantity and quality of skeletal muscle under physiological conditions. Male ddY mice (8 wk old) were orally administered β-carotene (0.5 mg once daily) for 14 d. Dietary β-carotene had no influence on body weight, but increased the soleus muscle/body weight ratio. <>The cross-sectional area (CSA) in muscle fibers of the soleus muscle was increased, indicating that administration of β-carotene induces muscle hypertrophy. In the soleus muscle of the β-carotene-administered mice, twitch force tended to be increased (p=0.06) and tetanic force was significantly increased, whereas specific force (force per CSA) remained unchanged. Dietary β-carotene increased the mRNA level of insulin-like growth factor 1 (Igf-1) as its splicing variant Igf-1ea, but had no influence on the liver Igf-1 mRNA level or serum IGF-1 level. β-Carotene promoted protein synthesis in the soleus muscle and reduced levels of ubiquitin conjugates, but had no influence on the mRNA levels of two atrogenes, Atrogin-1 and Murf1. On the other hand, β-carotene had no influence on the processing of the autophagy marker protein light chain 3.
<>These results indicate that in mice, administration of β-carotene increases mass and induces functional hypertrophy in the soleus muscle, perhaps by promoting IGF-1-mediated protein synthesis and by reducing ubiquitin-mediated protein degradation."[188]

[B] Although not a perfect example, Beta-Carotene appears to enhance bDNF.

"<>Autism-affected individuals are characterized by lower plasma oxytocin and its ectoenzyme regulator CD38. Oxytocin, a hypothalamic hormone secreted upon the release of CD38, plays a role in social behavior and bonding. All-trans retinoic acid is a potent inducer of CD38 and can be used as a novel therapeutic strategy in autism. We investigated the role of beta-carotene in rescuing autistic-like behavior in BALB/c and

BTBR mice. Beta-carotene derivatives are preferred as they are neither toxic nor teratogenic.
<>Beta-carotene at 0.1-5.0 mg/kg was administered orally to BALB/c and BTBR newborn mice on days 1-7. They were tested at age 2-3 months for five behavioral tests for "autism"; in addition, brain CD38, oxytocin, oxytocin receptor, Brain Derived Neurotrophic Factor (BDNF) and retinoic acid receptor gene expression, serum oxytocin levels, and neurological score were evaluated.
<>Beta-carotene administered at birth significantly increased T-maze alternations and led to longer time spent with an unfamiliar mouse in the "three-chamber test" and less time spent in the empty chamber. Furthermore, enhanced activity in the open field test; increased time spent in the reciprocal social interaction test; decreased grooming and bedding behaviors; and enhanced brain CD38, oxytocin, oxytocin receptor, BDNF, retinoic acid gene expression, and serum oxytocin levels. No changes in neurological score were observed. Beta-carotene oral supplementation to BALB/c and BTBR mice at birth significantly reduced restricted and stereotyped behaviors and interests, increased social interactions and communication, CD38, and oxytocin, probably by enhancing brain neuroplasticity without toxicity. Thus, beta-carotene administered after birth to newborns of families predisposed to "autism" has the potential to prevent/ameliorate" autistic like behavior". These results support further clinical studies."[189]

Potassium Chloride: Low POP

[A] Potassium is anabolic by promoting Leucine accretion.

"<>Following 7 d on K-deficient fodder the inhibition of growth and protein synthesis was closely correlated with the K content of the fodder (1-40 mmol/kg) and significant already at modest reductions in muscle K content. In vitro experiments with soleus muscle showed a linear relationship between the incorporation of [3H]leucine into muscle protein and K content, but the sensitivity to cellular K deficiency induced in vitro was much less pronounced than that induced in vivo. Thus, in soleus and extensor digitorum longus (EDL) muscles prepared from K-deficient rats, the incorporation of [3H]leucine was reduced by 30 and 47% respectively. This defect was completely restored by 24 h K repletion in vivo.
<>It is concluded that in the intact organism protein synthesis and growth are very sensitive to dietary K deficiency and that this can only partly be accounted for by the reduction in cellular K content per se. The observations emphasize the need for adequate K supplies to ensure optimum utilization of food elements for protein synthesis and growth."[190]

[B] Potassium Chloride (KCI) promotes IGF-1 expression.

“<>Skeletal muscle hypertrophy develops after intense training via many different mechanisms. Despite active investigations, they remain not fully understood. It stands to reason that compounds released from muscle cells during vigorous contraction may be

used in the process of skeletal muscle growth. We demonstrated that potassium chloride activates the expression of two splice forms of IGF-1 in muscle cells. Stimulation took place both at the mRNA and at the protein levels; it was observed in myoblasts and myotubes. Activation of growth factor expression was seen after incubation of cells at the KCl concentration of 7–12 mM for two hours, which is consistent with conditions existing during intensive muscle work. It should be noted that muscle exercise needs to be quite vigorous to achieve sufficiently high KCl concentrations for a relatively long time interval, which helps prevent unneeded myoblast proliferation in response to accidental noise. The observed stimulation was specific for potassium cation and not caused by an increase in osmotic pressure because sodium chloride at the same concentration did not activate growth factor expression or myoblast proliferation.
<>Myoblasts are not involved in muscle contraction but they play the key role in the processes of muscle hypertrophy development and regeneration after injury. Potassium chloride released from contracting myotubes may affect neighbouring myoblasts. In a similar manner, IGF-1 secreted by myotubes under the influence of KCl may activate the proliferation of myoblasts located in the proximity via a paracrine mechanism."[190.1]

L-Ornithine: Low POP

This amino acid is often overlooked, and it appears to be the very best "Cortisol Blocker" available, considering that its breakdown products enhance angiogenesis, making it a wise supplement to incorporate into each cycle.

[A] Ornithine reduces cortisol.

"<>Fifty-two apparently healthy Japanese adults who had previously felt slight stress as well as fatigue were recruited to be study participants and were randomly divided into either the L-ornithine (400 mg/day) or placebo group. They orally consumed the respective test substance every day for 8 weeks. Serum was collected for the assessment of cortisol and dehydroepiandrosterone-sulphate (DHEA-S). Perceived mood and quality of sleep were measured by the Profile of Mood States (POMS), Athens Insomnia Scale (AIS), and Ogri-Shirakawa-Azumi sleep inventory MA version (OSA-MA). Serum cortisol levels and the cortisol/DHEA-S ratio were significantly decreased in the L-ornithine group in comparison with the placebo group. Also, anger was reduced and perceived sleep quality was improved in the L-ornithine group."[191]

[A2] Ornithine, most likely through cortisol suppression, reduces anxiety.

"<>Intracerebroventricular injection of L-ornithine has demonstrated sedative and hypnotic effects in neonatal chicks exposed to acute stressful conditions. However, whether orally administered L-ornithine can reduce acute mental stress remains to be defined.
<>To clarify the nutritional importance of L-ornithine in controlling the stress response, in Experiment 1 we first investigated whether orally administered L-ornithine can be

transported into the brain of mice. Mice were orally administered L-ornithine (3 mmol/water 10 ml/kg, per os). L-Ornithine levels were significantly elevated in the cerebral cortex and hippocampus at 30 and 60 minutes post-administration. In Experiment 2, the effect of orally administered L-ornithine (0, 0.1875, 0.75 and 3 mmol/water 10 ml/kg, per os) on anxiety-like behavior in mice exposed to the elevated plus-maze test was examined at 30 minutes post-administration.
<>There was a significant increase in the percentage of time spent and entries in the open arms in the group receiving 0.75 mmol of L-ornithine compared to the control group. Furthermore, locomotion activity in a novel environment was not significantly changed between the control group and 0.75 mmol of L-ornithine group in Experiment 3. Therefore, it appears that orally administrated L-ornithine is bioavailable to the rodent brain and reduces anxiety-like behavior as demonstrated by the elevated plus-maze test."[191.1]

[B] Ornithine promotes protein synthesis by way of enhanced GH release (and cortisol inhibition).

"<>The purpose of this study was to determine whether ornithine affects the rate of tissue protein synthesis in male rats. Two experiments were done on five or two groups of young rats (5 wk) given diets containing 0.15, 0.3, 0.5 or 0.7% ornithine-HCl added to a 20% casein diet for 1 d (only one 3 h period) (Experiment 1), and given a diet containing 0 or 0.7% ornithine-HCl added to a 20% casein diet for 10 d (Experiment 2).
<>The plasma concentration of growth hormone (GH) was the highest in rats fed 0.5 and 0.7% ornithine added to the 20% casein diet. The fractional rates of protein synthesis in brain regions, liver and gastrocnemius muscle increased significantly with the 20% casein+0.7% ornithine diet compared with the 20% casein diet. In brain regions, liver and gastrocnemius muscle, the RNA activity [g protein synthesized/(g RNA·d)] significantly correlated with the fractional rate of protein synthesis. The RNA concentration (mg RNA/g protein) was not related to the fractional rate of protein synthesis in any organ.
<>The present results suggest that the treatment of young rats with ornithine is likely to increase the concentration of plasma GH and the rate of protein synthesis in the tissues, and that RNA activity is at least partly related to the fractional rate of tissue protein synthesis."[192]

Lactoferrin: High POP

A very intriguing chemical that is found in breast milk, it is a neuroprotective agent and myogenic supplement. Although it has a very short half-life at around twelve minutes it might be possible to consume it in the form of a drink to maintain steady blood concentrations, depending on concentration and subjective taste threshold.

[A] Lactoferrin promotes myogenesis by way of ERK1/2.

"<>Lactoferrin (Ltf), a naturally active glycoprotein, possesses anti-inflammatory, anti-microbial, anti-tumor, and immunomodulatory activities. Many published studies have indicated that Ltf modulates the proliferation of stem cells. However, the role of Ltf in the proliferation of satellite cells, an important cell type in muscle regeneration, has not yet been reported. Here, by using Ltf systemic knockout mice, we illustrate the role of Ltf in skeletal muscle.
<>Results shows that Ltf deficiency impaired proliferation of satellite cells (SCs) and the regenerative capability of skeletal muscle. Mechanistic studies showed that ERK1/2 phosphorylation was significantly downregulated after Ltf deletion in SCs. Simultaneously, the cell cycle-related proteins cyclin D and CDK4 were significantly downregulated. Intervention with exogenous recombinant lactoferrin (R-Ltf) at a concentration of 1000 μg/mL promoted proliferation of SCs.
<>In addition, intraperitoneal injection of Ltf effectively ameliorated the skeletal muscle of mice injured by 1.2% $BaCl_2$ solution. Our results suggest a protective effect of Ltf in the repair of skeletal muscle damage. Ltf holds promise as a novel therapeutic agent for skeletal muscle injuries."[194]

[B] Lactoferrin promotes bDNF expression.

"<>Lactoferrin (Lf) is a sialic acid (Sia)-rich, iron-binding milk glycoprotein that has multifunctional health benefits. Its potential role in neurodevelopment and cognition remains unknown. To test the hypothesis that Lf may function to improve neurodevelopment and cognition, the diet of postnatal piglets was supplemented with Lf from days 3 to 38. Expression levels of selected genes and their cognate protein profiles were quantitatively determined.
<>The importance of our new findings is that Lf (1) upregulated several canonical signaling pathways associated with neurodevelopment and cognition; (2) influenced ~10 genes involved in the brain-derived neurotrophin factor (BDNF) signaling pathway in the hippocampus and upregulated the expression of polysialic acid, a marker of neuroplasticity, cell migration and differentiation of progenitor cells, and the growth and targeting of axons; (3) upregulated transcriptional and translational levels of BDNF and increased phosphorylation of the cyclic adenosine monophosphate (cAMP) response element-binding protein, CREB, a downstream target of the BDNF signaling pathway, and a protein of crucial importance in neurodevelopment and cognition; and (4) enhanced the cognitive function and learning of piglets when tested in an eight-arm radial maze. The finding that Lf can improve neural development and cognition in postnatal piglets has not been previously described."[195]

B-Vitamins: Low POP

There is very limited toxicity of B-Vitamins, although most supplements contain far too much Cobalamin (B12), which being a natural NMDA antagonist is not good for cognition in healthy individuals. Taking a B-Complex every morning should be mandatory.

[A] Pyridoxine (B6) is myogenic.

"<>The expressions of myokines, such as IL-7, IL-8, secreted protein acidic and rich in cysteine, IL-6, growth differentiation factor 11, myonectin, leukaemia inhibitory factor, apelin and retinoic acid receptor responder (tazarotene induced) 1, the expression of Nrf2 and its regulated factors, such as heme oxygenase 1, superoxide dismutase 2, glutathione peroxidase 1 and glutathione S-transferase, and the expression of myogenin and HSP60 were significantly elevated in the 7 mg/kg PN HCl group compared with the 1 mg/kg PN HCl diet ($P<0.05$). No significant differences in levels of these genes were observed between the 35 and 1 mg/kg PN HCl, with the exception of GDF11 and myonectin, whose expressions were significantly increased in the 35 mg/kg PN HCl ($P<0.05$).
<>Notably, the majority of gene expressions that were affected responded to dietary supplemental vitamin B6 in a similar manner. The results suggest that compared with the marginal vitamin B6 deficiency, the recommended dietary intake of vitamin B6 upregulates the gene expression of a number of factors that promote the growth and repair of skeletal muscle."[200]

[B] Thiamine is the most important B-Vitamin for neuroprotective / neurotrophic purposes, not Cobalamin (B12). (TD = Thiamine Deficiency)

"<>TD affects multiple organ systems, including the cardiovascular, muscular, gastrointestinal, and central and peripheral nervous systems. In the brain, TD causes a cascade of events including mild impairment of oxidative metabolism, neuroinflammation and neurodegeneration, which are commonly observed in neurodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). Thiamine metabolites may serve as promising biomarkers for neurodegenerative diseases and thiamine supplementations exhibit therapeutic potential for patients of some neurodegenerative diseases."[201]

[C] Folate promotes myogenesis.

"<>We found that folic acid promoted the formation of multinucleated myotubes, and increased the fusion index and creatine kinase (CK) activity in a concentration-dependent manner. In addition, western blot analysis revealed that the expression levels of the muscle-specific marker, myosin heavy chain (MyHC), as well as those of the myogenic regulatory factors (MRFs), MyoD and myogenin, were increased in the folic acid-treated myotubes during myogenic differentiation.
<>Folic acid also promoted the activation of the Akt pathway, and this effect was inhibited by treatment of the C2C12 cells with LY294002 (Akt inhibitor). Blocking of the Akt pathway with a specific inhibitor revealed that it was necessary for mediating the stimulatory effects of folic acid on muscle cell differentiation and fusion. Taken together, our data suggest that folic acid promotes the differentiation of C2C12 cells through the activation of the Akt pathway."[202]

[D] Exercise enhances the excretion of B-Vitamins.

"<>Regular moderate exercise training increased urinary excretion of thiamin. Dietary intakes and urinary excretions of thiamin and riboflavin showed positive correlation in both the exercise training and non-exercise training groups as the exercise training period went by, while the correlations in the exercise training group were weaker than those in the non-exercise training group. Therefore, regular exercise training can alter the urinary excretion of thiamin and riboflavin in rats."[203]

Vitamin D3: Low POP

[A] Vitamin D3 is associated with neurogenesis in aging.

"<>Vitamin D supplementation significantly mitigated the observed aging-related reduction in brain BDNF level and activities of AChE and antioxidant enzymes and elevation in malondialdehyde level and caspase-3 activity compared to control groups. Brain BDNF level correlated positively with serum 25(OH) D level and brain AChE activity and negatively with brain malondialdehyde level and caspase-3 activity in supplemented groups.
<>Conclusion: Restoring vitamin D levels may, therefore, represent a useful strategy for healthy brain aging. Augmenting brain BDNF seems to be a key mechanism through which vitamin D counteracts age-related brain dysfunction."[204]

[B] Vitamin D3 reduces MRF's but increases hypertrophy through stimulation protein accretion, and this makes it an essential nutrient for periods of longer programmed detraining.

"<>Vitamin D, a fat-soluble vitamin, is an important nutrient for tissue homeostasis and is recently gaining attention for its role in sarcopenia. Although several studies have focused on the role of vitamin D in muscle homeostasis, the molecular mechanism underlying its action on skeletal muscle remains unclear. This study investigated the role of vitamin D in myogenesis and muscle fiber maintenance in an immortalized mouse myogenic cell line. A high concentration of active vitamin D, 1α,25(OH)2D3, decreased the expression of myogenic regulatory factors (MRFs), myf5 and myogenin in proliferating myoblasts.
<>In addition, high concentration of vitamin D reduced myoblast-to-myoblast and myoblast-to-myotube fusion through the inhibition of Tmem8c (myomaker) and Gm7325 (myomerger), which encode muscle-specific fusion-related micropeptides. A similar inhibitory effect of vitamin D was also observed in immortalized human myogenic cells. A high concentration of vitamin D also induced hypertrophy of multinucleated myotubes by stimulating protein anabolism. The results from this study indicated that vitamin D had both positive and negative effects on muscle homeostasis, such as in muscle regeneration and myofiber maintenance."[205]

Selenium: Low POP

Selenium enhances slow twitch fiber growth.

"<>Background: The purpose of the present study was to evaluate the effect of sodium selenite on skeletal and cardiac muscular function in patients with severe Se deficiency. <>Methods: Skeletal and cardiac muscular function was investigated in 10 selenium depleted patients on long-term home parenteral nutrition because of short bowel syndrome. The following examinations were applied: Skeletal muscle biopsy, muscular force test (Kin-Com dynamometer test), electromyography (EMG) and radionuclide ventriculography. The patients were blindly randomized to intravenous supplementation with selenium 200 micrograms 5 to 7 times per week or placebo for 4 months. Hereafter the examinations were repeated. The patients randomized to placebo received selenium in an open study for a further 4 months and hereafter their skeletal and cardiac function was reevaluated.
<>Results: Plasma selenium increased to normal levels from median .21 mumol/l (range 0-.69) to 1.25 mumol/l (range .9-2.27) following selenium repletion. The muscle biopsies showed only minor abnormalities. The only change after selenium supplementation was a small but statistically significant increase of the mean diameter of fiber type 1. The muscle strength of the quadriceps muscle was unchanged after selenium substitution. EMG did not reveal signs of myopathy."[210]

Zinc: Low POP

Zinc is myogenic through enhancing complete myogenesis.

"<>Myogenic regeneration occurs through a chain of events beginning with the output of satellite cells from quiescent state, formation of competent myoblasts and later fusion and differentiation into myofibres. Traditionally, growth factors are used to stimulate muscle regeneration but this involves serious off-target effects, including alterations in cell homeostasis and cancer. In this work, we have studied the use of zinc to trigger myogenic differentiation.
<>We show that zinc promotes myoblast proliferation, differentiation and maturation of myofibres. We demonstrate that this process occurs through the PI3K/Akt pathway, via zinc stimulation of transporter Zip7. Depletion of zinc transporter Zip7 by RNA interference shows reduction of both PI3K/Akt signalling and a significant reduction of multinucleated myofibres and myotubes development. Moreover, we show that mature myofibres, obtained through stimulation with high concentrations of zinc, accumulate zinc and so we hypothesise their function as zinc reservoirs into the cell."[211]

Lithium Orotate (or Prescribed as Carbonate): Low POP

Lithium should be considered an essential mineral; in low dosages it is extremely beneficial towards mind and body by inhibiting GSK3B, a gene that suppresses MRF

release and Neurogenesis. Importantly, Lithium increases B-Catenin, which as you have learned promotes Myogenic Differentiation at the expense of accelerated muscle stem cell aging, although surely a lower dosage of Lithium will not substantially affect B-Catenin, and therefore should be of no worry.

The primary concern with prescribed Lithium is that the “therapeutic level” many doctors pursue in their patients is too high of a blood level, there is no reason to exceed 300mg of Lithium per day. When Lithium is taken in dosages over 600mg side effects begin to present themselves, such as thyroid toxicity, electrolyte imbalances, and lethargy.

You can purchase Lithium on Amazon without a prescription, although Orotic Acid is toxic, at the time of writing this book there are no other forms available over-the-counter aside from prescription.

[A] Lithium is myogenic through promoting IGF-1 by inhibiting GSK3B.

"<>Skeletal muscle atrophy is a prominent and disabling feature of chronic wasting diseases. Prevention or reversal of muscle atrophy by administration of skeletal muscle growth (hypertrophy)-stimulating agents such as insulin-like growth factor I (IGF-I) could be an important therapeutic strategy in these diseases. To elucidate the IGF-I signal transduction responsible for muscle formation (myogenesis) during muscle growth and regeneration, we applied IGF-I to differentiating C(2)C(12) myoblasts and evaluated the effects on phosphatidylinositol 3-kinase (PI3K)/Akt/glycogen synthase kinase-3beta (GSK-3beta) signaling and myogenesis. IGF-I caused phosphorylation and inactivation of GSK-3beta activity via signaling through the PI3K/Akt pathway.
<>We assessed whether pharmacological inhibition of GSK-3beta with lithium chloride (LiCl) was sufficient to stimulate myogenesis. Addition of IGF-I or LiCl stimulated myogenesis, evidenced by increased myotube formation, muscle creatine kinase (MCK) activity, and troponin I (TnI) promoter transactivation during differentiation. Moreover, mRNAs encoding MyoD, Myf-5, myogenin, TnI-slow, TnI-fast, MCK, and myoglobin were upregulated in myoblasts differentiated in the presence of IGF-I or LiCl. Importantly, blockade of GSK-3beta inhibition abrogated IGF-I- but not LiCl-dependent stimulation of myogenic mRNA accumulation, suggesting that the promyogenic effects of IGF-I require GSK-3beta inactivation and revealing an important negative regulatory role for GSK-3beta in myogenesis. Therefore, this study identifies GSK-3beta as a potential target for pharmacological stimulation of muscle growth."[214.1]

[B] Lithium (LiCl) reduces muscle atrophy factors.

"<>Most recent studies reported that FoxO1 transcription factor was a negative regulator of myogenesis under serum withdrawal condition, a situation not actually found in vivo. Therefore, the role of FoxO1 in myogenesis should be re-examined under more physiologically relevant conditions. Here we found that FoxO1 was preferentially localized to nucleus in proliferating (PMB) and confluent myoblasts (CMB) and its

nuclear exclusion was a prerequisite for formation of multinucleated myotubes (MT). The nuclear shuttling of FoxO1 in PMB could be prevented by leptomycin B and we further found that cytoplasmic accumulation of FoxO1 in myotubes was caused by the blockade of its nuclear import. Although over-expression of wildtype *FoxO1* in C2C12 myoblasts significantly blocked their myogenic differentiation under serum withdrawal condition, application of insulin and LiCl, an activator of Wnt signaling pathway, to these cells successfully rescued their myogenic differentiation and generated myotubes with larger diameters. <>Interestingly, insulin treatment significantly reduced FoxO1 level and also delayed nuclear re-accumulation of FoxO1 triggered by mitogen deprivation. We further found that FoxO1 directly repressed the promoter activity of myogenic genes and this repression can be relieved by insulin and LiCl treatment. These results suggest that FoxO1 inhibits myogenesis in serum withdrawal condition but turns into a hypertrophy potentiator when other myogenic signals, such as Wnt and insulin, are available."[214.2]

[C] Lithium promotes NGF release.

"<>There is compelling evidence that withdrawal of neurotrophins can lead to impaired neuronal function and even apoptotic death of neurons. Recent experimental evidence suggests that antidepressant drugs and electroconvulsive treatment might work by enhancing CNS levels of neurotrophins. In addition, Lithium (LI) has been shown to exert robust neuroprotective effects apart from its well known mood-stabilizing effects in humans.
<>In this study we investigated the effects of subchronic (14 days) treatment with various doses of LI on the NGF content of several regions of the adult rat brain. LI treatment, which resulted in prophylactic LI serum concentrations (0.72 +/- 0.08 mMol l(-1)), induced a significant ($P < 0.05$) increase in NGF concentrations in the frontal cortex (+23.2%), hippocampus (+72%), amygdala (+74%) and limbic forebrain (+46.7%) compared to untreated controls, whereas no effects on NGF concentrations were observed in the striatum, the hypothalamus or the midbrain, even using various LI doses. Moreover, no significant change in NGF concentrations in the frontal cortex was observed after acute (1 day) treatment with LI. Our findings lend support to the notion that an enhancement of NGF production may be specifically involved in the mechanisms of action of antibipolar treatments."[214.3]

[D] Lithium downregulates GSK3B expression, which is of vital importance as prophylaxis against the development of numerous often-fatal neurodegenerative diseases such as the Dementias, & Parkinsons. When will doctors begin using Lithium for its true neurotrophic purposes, and not just to "stabilize moods"?

"<>Background: There is evidence of increased systemic expression of active GSK3B in Alzheimer's disease patients, which apparently is associated with the formation of senile

plaques and neurofibrillary tangles. Due to its central role in the pathogenesis of AD, GSK3B is currently a promising target of the pharmaceutical industry. Whilst trials with specific GSK inhibitors in AD are under way, major attention has been focused on the neuroprotective effects of lithium. Whereas the direct and indirect inhibitory effects of lithium over GSK3 activity have been documented by several groups, its effects over Gsk3 transcription have not yet been addressed.
<>Methods: We used quantitative PCR to evaluate the transcriptional regulation of Gsk3a and Gsk3b in lithium-treated primary cultures of rat cortical and hippocampal neurons.
<>Results: We found a significant and dose-dependent reduction in the expression of Gsk3b, which was specific to hippocampal cells. This same effect was further confirmed in vivo by measuring Gsk3 expression in different brain regions and in peripheral leukocytes of adult rats treated with lithium.
<>Conclusion: Our studies show that LiCl can modulate Gsk3b transcription in vitro and in vivo. This observation suggest new regulatory effects of lithium over Gsk3b, contributing to the better understanding of its mechanisms of action, offering a new and complementary explanation for Gsk3b modulation and reinforcing its potential for the inhibition of key pathological pathways in Alzheimer's disease."[214.4]

Melatonin: Low POP

Melatonin should be considered an Essential Nutrient, considering our Pineal Gland loses close to 10% of its ability to produce Melatonin per ten years. When people talk about the Pineal Gland as being a conduit to the soul, the "Third Eye", or as a way to enhance consciousness they are correct but tend to misunderstand the neurotrophic vs psychotropic value of Melatonin. Melatonin will enhance the intelligence of a human by promoting healthy circadian rhythms, circadian genes, slow wave sleep, neurogenesis, and through systemic antioxidant effects. The use of Melatonin should be mandatory for anyone who wishes to delay aging, or partially counteract the deleterious effects of recreational drugs, or psychological stress.

[A] Melatonin enhances neurogenesis.

"<>Regulation of adult hippocampal neurogenesis is influenced by circadian rhythm, affected by the manipulation of sleep, and is disturbed in animal models of affective disorders. These observations and the link between dysregulation of the circadian production of melatonin and neuropsychiatric disorders prompted us to investigate the potential role of melatonin in controlling adult hippocampal neurogenesis. In vitro, melatonin increased the number of new neurons derived from adult hippocampal neural precursor cells in vitro by promoting cell survival.
<>This effect was partially dependent on the activation of melatonin receptors as it could be blocked by the application of receptor antagonist luzindole. There was no effect of

melatonin on cell proliferation. Similarly, in the dentate gyrus of adult C57BL/6 mice in vivo, exogenous melatonin (8 mg/kg) also increased the survival of neuronal progenitor cells and post-mitotic immature neurons. Melatonin did not affect precursor cell proliferation in vivo and also did not influence neuronal and glial cell maturation. Moreover, melatonin showed antidepressant-like effects in the Porsolt forced swim test. These results indicate that melatonin through its receptor can modulate the survival of newborn neurons in the adult hippocampus, making it the first known exogenously applicable substance with such specificity."[215]

[B] Melatonin reduces intramuscular lipid accumulation.

"<>In obesity and diabetes, intramuscular fat (IMF) content correlates markedly with insulin sensitivity, which makes IMF manipulation an area of therapeutic interest. Melatonin, an important circadian rhythm-regulating hormone, reportedly regulates fat deposition, but its effects on different types of adipose vary. Little is known about the role of melatonin in IMF deposition. Here, using intramuscular preadipocytes in pigs, we investigated to determine whether melatonin affects or regulates IMF deposition. We found that melatonin greatly inhibited porcine intramuscular preadipocyte proliferation. Although melatonin administration significantly upregulated the expression of adipogenic genes, smaller lipid droplets were formed in intramuscular adipocytes. Additional investigation demonstrated that melatonin promoted lipolysis of IMF by activating protein kinase A and the signaling of ERK1/2.
<>Moreover, melatonin increased thermogenesis in intramuscular adipocytes by enhancing mitochondrial biogenesis and mitochondrial respiration. A mouse model, in which untreated controls were compared with mice that received 3 weeks of melatonin treatment, verified the effect of melatonin on IMF deposition. In conclusion, melatonin reduces IMF deposition by upregulating lipolysis and mitochondrial bioactivities. These data establish a link between melatonin signaling and lipid metabolism in mammalian models and suggest the potential for melatonin administration to treat or prevent obesity and related diseases."[216]

[C] Melatonin protects myoblasts against apoptosis through mitochondrial biogenesis.

"<>It is known that, besides a wide range of functions, melatonin provides protection against oxidative stress, thanks to its ability to act, directly, as a free radical scavenger and, indirectly, by stimulating antioxidant enzymes production and mitochondrial electron transport chain efficiency. Oxidative stress is one of the major players in initiating apoptotic cell death in skeletal muscle, as well as in other tissues. Apoptosis is essential for skeletal muscle development and homeostasis; nevertheless, its misregulation has been frequently observed in several myopathies, in sarcopenia, as well as in denervation and disuse.
<>Melatonin activity was investigated in undifferentiated C2C12 skeletal muscle cells, after exposure to various apoptotic chemical triggers, chosen for their different

mechanisms of action. Cells were pretreated with melatonin and then exposed to hydrogen peroxide, etoposide and staurosporine.
<>Morphofunctional and molecular analyses show that in myoblasts melatonin prevents oxidative stress and apoptosis induced by chemicals following, at least in part, the mitochondria pathway. These results confirm melatonin ability to act as an antioxidant and antiapoptotic molecule in skeletal muscle cells, thus suggesting a possible therapeutic strategy for myopathies involving apoptosis misregulation."[217]

[D] Melatonin is anti-fibrotic by reducing pro-inflammatory cytokine production and myogenic through enhancing PGC1a expression.

"<>Ischemic injury is a major risk factor for fibrosis. However, the precise mechanisms by which fibrosis is regulated and induced under ischemic oxidative stress conditions are unknown. To address this, we investigated the effect of melatonin on ischemia-induced fibrosis. In a hindlimb ischemia mouse model, ischemia induced fibrosis by increasing inflammation and the expression of extracellular matrix (ECM) proteins.
<>Melatonin prevented ischemia-induced fibrosis in the injured tissues. In particular, melatonin suppressed the fibrosis-mediated inflammatory reaction in myoblasts through the microRNA-149 (miR-149)/indoleamine 2,3-dioxygenase-1 (IDO-1) signaling pathway. The melatonin-induced increase in miR-149 inhibited the expression of the pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) and ECM components, such as collagen I and fibronectin.
<>In addition, melatonin increased antioxidative activity and mitochondrial function in myoblasts via the miR-149/peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) signaling axis, and the anti-fibrotic effects of melatonin were blocked by inhibition of miR-149. These findings indicate that melatonin is a key target molecule in fibrosis related to ischemic diseases and that miR-149 might be a novel target for the treatment of ischemia-induced fibrosis."[218]

Rooibos Tea: Moderate POP

Aspalathus Linearis (Rooibos) is an underappreciated herb that contains many antioxidant compounds.

[A] Rooibos Tea appears to be one of the strongest over-the-counter Cortisol inhibitors.

"<>Scope: To determine the effect of Rooibos (Aspalathus linearis) on glucocorticoid biosynthesis and inactivation in vivo and in vitro.
<>Methods and results: Ultra-performance liquid chromatography/tandem mass spectrometry (UPLC-MS/MS) analyses of in vivo studies showed that human Rooibos consumption increased cortisone plasma levels in males ($p = 0.0465$) and reduced cortisol:cortisone ratios in males and females ($p = 0.0486$) at risk for cardiovascular disease. In rats, corticosterone (CORT) ($p = 0.0275$) and deoxycorticosterone ($p = 0.0298$) levels as well as the CORT:testosterone ratio ($p = 0.0009$) decreased following

Rooibos consumption. The inactivation of cortisol was investigated in vitro by expressing 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1) and type 2 (11βHSD2) in CHO-K1 cells. Rooibos inhibited 11βHSD1, which resulted in a significant reduction in the cortisol:cortisone ratio ($p < 0.01$). No significant effect was detected on 11βHSD2. In vitro studies in adrenal H295R cells showed that Rooibos and rutin, one of the more stable flavonoid compounds present in Rooibos, significantly reduced the levels of cortisol and CORT in cells stimulated with forskolin to mimic a stress response. <>Conclusion: In vivo studies demonstrate that Rooibos significantly decreased glucocorticoid levels in rats and steroid metabolite ratios linked to metabolic disorders--cortisol:cortisone in humans and CORT:testosterone in rats. Results obtained at cellular level elucidate possible mechanisms by which these effects were achieved."[218.1]

[B] Rooibos Tea contains many antioxidant phytochemicals, and these chemicals display similar chromosomal protection against toxins (MMC / BAP) to Green Tea, and its varieties. In certain scenarios Rooibos Tea offers increased protection to chromosomes over Green Tea. It may be an intelligent idea to mix different teas together, such as Camellia Sinensis Tea + Rooibos, et cetera.

"<>The suppressing effects of crude extracts of three kinds of tea - green tea (GT) from Japan, Po-lei tea (PT) from China, and Rooibos tea (RT) from South Africa - on the induction of chromosome aberrations in cultured CHO cells and mice were studied. When CHO cells were exposed to each tea extract in the presence of rat liver microsomal enzymes (S9 mix) together with benzo[a]pyrene (B(a)P) or mitomycin C (MMC), a decrease in the frequency of chromosome aberrations was observed. PT and RT, but not GT, also suppressed the induction of chromosome aberrations by MMC in the absence of S9 mix. When cells were treated with tea extract after B(a)P or MMC treatment, RT suppressed the induction of chromosome aberrations in the presence and absence of S9 mix whereas GT and PT showed suppressing effects only in the presence of S9 mix. <>These data suggest that catechines, well-known antimutagens in tea samples, might account for the inhibitory effect in the case of GT and PT. Since RT contains few catechines, several unknown antimutagenic components could be responsible for its effect.
<>The antimutagenic effects of tea extracts at concentration levels consumed by humans were examined in mice using micronucleus induction with B(a)P or MMC. When mice received oral gavage of 0.2% GT, 0.1% PT, and 0.1% RT at 1.0 ml/mouse 6 h before intraperitoneal injection of MMC, a decrease in the frequency of micronuclei was observed. The induction of micronuclei by B(a)P was suppressed by oral dosage of GT, PT and RT at 1.0 ml/mouse/day for 28 days. This was not due to a delay in the maturation of micronucleated reticulocytes. In conclusion, intake of tea might suppress the mutagenic activity of certain potent mutagens in human beings."[218.2]

Kombucha: Low POP

Kombucha serves two purposes, the first is as a probiotic, the second is as a source of Low-Dose Alcohol. Kombucha promotes the growth of Lactobacillus.

"<>Non-alcoholic fatty liver disease (NAFLD) is one of the most common liver disorders. Possible links have been recently found between the gut-microbiota and the host metabolism in development of NAFLD and obesity. Therefore, understanding the changes in intestinal microbiota during the progression of NAFLD, is important. <>In this study, the effect of Kombucha tea (KT), obtained by microbial fermentation of sugared black tea, was investigated on gut-microbiota during the progression of NAFLD. The results indicated a decrease in Erysipelotrichia class by treatment with KT in comparison to the methionine/choline-deficient (MCD)-fed db/db mice. Allobaculum, Turicibacter, and Clostridium genera, were only detected in MCD-fed db/db mice and were decreased after treatment with KT, whereas Lactobacillus was more abundant in MCD + KT-fed mice than in MCD only-fed mice and Mucispirillum, was found only in the MCD + KT-fed mice group. Our results demonstrated that the change of intestinal microbiota was influenced by KT intake, contributing to combat NAFLD."[219]

Sulforaphane (Broccoli Sprouts): Moderate-High POP

Broccoli Sprouts are a superb antioxidant after a certain chemical reaction occurs within them. A chemical contained within broccoli sprouts called Glucoraphanin transforms into Sulforaphane upon cellular damage to the plant structure (carbohydrates) sustained during chewing or blending.
If you do not wish to purchase Sulforaphane extracts, and instead consume broccoli sprouts, remember that the concentration of Glucoraphanin progressively decreases as broccoli matures, making it very important that you grow your own Broccoli Sprouts or purchase them at store over using mature Broccoli florets. I would suggest adding it to a daily blended shake with brown mustard powder or add them onto each meal.

[A] Sulforaphane is a Myostatin Inhibitor by way of Histone Deacetylase Inhibition.

"<>Satellite cells function as skeletal muscle stem cells to support postnatal muscle growth and regeneration following injury or disease. There is great promise for the improvement of muscle performance in livestock and for the therapy of muscle pathologies in humans by the targeting of myostatin (MSTN) in this cell population. Human diet contains many histone deacetylase (HDAC) inhibitors, such as the bioactive component sulforaphane (SFN), whose epigenetic effects on MSTN gene in satellite cells are unknown.
<>Therefore, we aimed to investigate the epigenetic influences of SFN on the MSTN gene in satellite cells. The present work provides the first evidence, which is distinct from the effects of trichostatin A (TSA), that SFN supplementation in vitro not only acts as a HDAC inhibitor but also as a DNA methyltransferase (DNMT) inhibitor in porcine

satellite cells. Compared with TSA and 5-aza-2'-deoxycytidine (5-aza-dC), SFN treatment significantly represses MSTN expression, accompanied by strongly attenuated expression of negative feedback inhibitors of the MSTN signaling pathway. miRNAs targeting MSTN are not implicated in posttranscriptional regulation of MSTN. Nevertheless, a weakly enriched myoblast determination (MyoD) protein associated with diminished histone acetylation in the MyoD binding site located in the MSTN promoter region may contribute to the transcriptional repression of MSTN by SFN. These findings reveal a new mode of epigenetic repression of MSTN by the bioactive compound SFN. This novel pharmacological, biological activity of SFN in satellite cells may thus allow for the development of novel approaches to weaken the MSTN signaling pathway, both for therapies of human skeletal muscle disorders and for livestock production improvement."[219.1]

[B] Sulforaphane promotes MyoD & reduces the muscle atrophy factor Atrogin-1.

"<>Muscle atrophy occurs in various catabolic conditions, including hormone imbalance, severe injury, sepsis, cancer, and aging. Dexamethasone (DEX) is a synthetic glucocorticoid and is used an anti-inflammatory agent. However, when chronically used, it is accompanied by side effects, such as, muscle atrophy, diabetes mellitus, and obesity. <>In this study, we investigated the effect of sulforaphane (SFN) on DEX-induced muscle atrophy and the underlying mechanisms involved. DEX induced muscle atrophy was accompanied by increased muscle specific ubiquitin E3 ligase markers, such as, Atrogin-1 and myostatin, and decreased MyoD in C2C12 myotubes. To investigate the role played by SFN in DEX-induced muscle atrophy, we quantified mRNA levels of muscle atrophy markers, protein synthesis using a puromycin incorporation assay, protein degradation by ubiquitination, and myotube diameters by PAS staining in C2C12 myotubes co-treated with DEX and SFN.
<>Interestingly, SFN effectively prevented myostatin and Atrogin-1 mRNA upregulations by DEX, increased the mRNA level of MyoD, and consequently, reduced protein degradation. Furthermore, SFN enhanced protein synthesis through a Foxo-dependent pathway by activating Akt, and thus, increased myotube diameters. These results show SFN inhibits DEX-induced muscle atrophy in C2C12 myotubes via Akt/Foxo signaling."[219.2]

[C] Sulforaphane enhances Long Term Potentiation.

"<>Increases in human life expectancy have led to increases in the prevalence of senile dementia and neurodegenerative diseases. This is a major problem because there are no curative treatments for these diseases, and patients with unmanaged cognitive and neurodegenerative symptoms experience many social problems. Sulforaphane is a type of organosulfur compound known as an isothiocyanate. It is derived from glucoraphanin, a compound found in cruciferous vegetables such as broccoli, brussels sprouts, and cabbages, via an enzymatic reaction that is triggered by plant damage (e.g., chewing).

Sulforaphane exhibits activity against cancer, inflammation, depression, and severe cardiac diseases. It can also alleviate oxidative stress and neural dysfunction in the brain. However, there is insufficient knowledge about the electrophysiological and behavioral basis of the effects of sulforaphane on learning and memory.
<>Therefore, we evaluated whether acute sulforaphane administration affected long-term potentiation (LTP) in organotypic cultured rat hippocampal tissues. We also measured the effect of sulforaphane on the performance of three behavioral tests, the Y-maze test, the passive avoidance test, and the Morris water maze, which assess short-term memory, avoidance memory, and short and long-term spatial memory, respectively. We found that sulforaphane increased the total field excitatory postsynaptic potential (fEPSP) in a dose-dependent manner after high frequency stimulation and attenuated scopolamine-induced interference of the fEPSP in the hippocampal CA1 area. Sulforaphane also restored cognitive function and inhibited memory impairment as indicated by the alleviation of the negative neurological effects of scopolamine, i.e, a lowered ratio of spontaneous alternation in the Y-maze, a reduced step-through latency in the passive avoidance test, and an increased navigation time in the Morris water maze.
<>These results indicate that sulforaphane can effectively prevent the attenuation of LTP and cognitive abilities induced by cholinergic and muscarinic receptor blockade. Further research is warranted to explore the potential therapeutic and prophylactic utility of sulforaphane for improving learning and memory, especially in those suffering from neurodegenerative disorders."[219.3]

[D] Brown Mustard Seed Powder enhances Sulforaphane generation when added to Broccoli meals. Do not confuse Sulforaphane-NAC with N-acetyl-l-cysteine, they are separate chemicals. N-acetyl-l-cysteine is a great antioxidant but may promote BBB breakdown[219.3.1], and thus I have not included it in this book as a supplement, as there are many alternative antioxidants.

"<>Scope: Broccoli contains glucosinolate glucoraphanin, which, in the presence of myrosinase, can hydrolyze to isothiocyanate sulforaphane, reported to have anticarcinogenic activity. However, the myrosinase enzyme is denatured on cooking. Addition of an active source of myrosinase, such as from powdered mustard seed, to cooked Brassica vegetables can increase the release of health beneficial isothiocyanates; however, this has not previously been proven in vivo.
<>Methods and results: The concentration of sulforaphane metabolite (sulforaphane N-acetyl-l-cysteine [SF-NAC]) in 12 healthy adults after the consumption of 200 g cooked broccoli, with and without 1 g powdered brown mustard, was studied in a randomized crossover design. During the 24-h period following the consumption of the study sample, all urine was collected. SF-NAC content was assayed by HPLC. When study subjects ingested cooked broccoli alone, mean urinary SF-NAC excreted was 9.8 ± 5.1 μmol per g creatinine, and when cooked broccoli was consumed with mustard powder, this increased significantly to 44.7 ± 33.9 μmol SF-NAC per gram creatinine.

<>Conclusion: These results conclude that when powdered brown mustard is added to cooked broccoli, the bioavailability of sulforaphane is over four times greater than that from cooked broccoli ingested alone."[219.4]

Sublingual Glutathione: High POP

"<>Glutathione (GSH) is critical to fight against oxidative stress. It's very low bioavailability limits the interest of [it for] supplementation. The purpose of this study was to compare the bioavailability, the effect on oxidative stress markers and the safety of a new sublingual form of GSH with two commonly used dietary supplements, N-acetylcysteine (NAC) and oral GSH. The study was a three-week randomized crossover trial. 20 Volunteers with metabolic syndrome were enrolled. GSH levels and several oxidative stress markers were determined at different times during each 21-days period. Compared to oral GSH group, an increase of total and reduced GSH levels in plasma and a higher GSH/GSSG ratio (p=0.003) was observed in sublingual GSH group. After 3 weeks of administration, there was a significant increase of vitamin E level in plasma only in sublingual GSH group (0.83 µmol/g; p=0.04). Our results demonstrate the superiority of a new sublingual form of GSH over the oral GSH form and NAC in terms of GSH supplementation."[220]

Chromium III (Picolinate): Low POP

[A] Chromium enhances UCP3.
[See: Anti-Inflammation Dietary Fats: MCT oil]

"<>The aim of this study was to evaluate the impact of three different chromium forms as chromic chloride (CrCl), chromium picolinate (CrPic), and a newly synthesized complex of chromium chelated with small peptides (CrSP) on glucose uptake and metabolism in vitro. In cultured skeletal muscle cells, chromium augmented insulin-stimulated glucose uptake and metabolism as assessed by a reduced glucose concentration of culture medium. At the molecular level, insulin significantly increased the mRNA levels of insulin receptor (IR), glucose transporter 4 (GLUT4), glycogen synthase (GS), and uncoupling protein-3 (UCP3), and these impacts can be enhanced by the addition of chromium, especially in the form of CrSP. Collectively, results of this study demonstrate that chromium improves glucose uptake and metabolism through upregulating the mRNA levels of IR, GLUT4, GS, and UCP3 in skeletal muscle cells, and CrSP has higher efficacy on glucose uptake and metabolism compared to the forms of CrCl and CrPic."[220.0]

[B] Chromium enhances Insulin's anabolic effect on muscle cells.

"<>The aim of this study was to evaluate the impact of three different chromium forms--chromic chloride ($CrCl_3$), chromium picolinate (CrPic), and a newly synthesized

complex of chromium chelated with small peptides (CrSP)--on protein metabolism in vitro. In cultured skeletal muscle cells, CrSP was able to increase the basal and insulin-stimulated levels of protein deposition in skeletal muscles cells. $CrCl_3$ and CrPic augmented insulin-stimulated protein synthesis. At the molecular level, insulin significantly increased the mRNA levels of insulin-like growth factor 1 and insulin-like growth factor 1 receptor. These impacts could be enhanced by the addition of chromium, especially CrSP. The mRNA levels of ubiquitin were significantly reduced when cells were cultured with chromium or/and insulin. Assuming that the mRNA level increase or decrease results in increased or decreased levels of these proteins, chromium would improve protein anabolism and reduce protein catabolism."[220.B]

[C] Chromium reduces intramuscular lipids and promotes muscle growth.

"<>An experiment was conducted to evaluate the effects of chromium picolinate (CrP) on growth performance, carcass composition, and tissue accretion rates in pigs from 27 to 109 kg BW. Seven littermate sets of Yorkshire-Hampshire barrows, individually penned, were fed a fortified, corn-soybean meal basal diet (.95% lysine from 27 to 55 kg; .80% lysine from 55 to 109 kg) supplemented with 0 or 200 micrograms/kg of Cr from CrP. Addition of CrP increased ($P < .09$) ADG but did not affect ADFI or feed:gain ratio. Average and 10th rib backfat and longissimus muscle area were not affected by Cr supplementation. The right side of the carcass was physically dissected into muscle, fat, bone, and skin. Additionally, five pigs were killed for determination of initial body composition.
<>Dietary CrP addition increased ($P < .02$) the percentage of muscle and decreased ($P < .06$) the percentage of fat. Total gain of dissected bone and skin were not different between treatments, but CrP increased ($P < .06$) the total gain of dissected muscle and decreased ($P < .02$) the total gain of dissected fat. Also, CrP increased the daily accretion rates of muscle ($P < .05$) and bone ($P < .03$) and decreased the daily accretion rate of fat ($P < .05$). The left side of the carcass was ground for determination of water, protein, lipid, and ash. The addition of CrP to the diet increased the percentage ($P < .09$) and accretion rate ($P < .09$) of water and increased the percentage ($P < .004$), total gain ($P < .02$), and accretion rate ($P < .02$) of protein while decreasing ($P < .04$) the percentage of lipid. Pigs fed CrP also had a decreased ($P < .004$) percentage of lipid in the dissected carcass muscle. Water, protein, and ash from the dissected muscle were not different between treatments.
<>These results suggest that CrP supplementation throughout the entire growing-finishing phase increases the total gain and accretion rate of muscle while decreasing the total gain and accretion rate of fat. This results in carcasses with an increased percentage of muscle and decreased percentage of fat."[220.C]

Caffeine: Low POP

A paradoxical (both Pro-Inflammatory & Anti-Inflammatory) chemical, it should be combined with L-Theanine (Read on), Agmatine[221.00], Ascorbic Acid[221.01], L-Carnitine[221.02), Lithium[221.03], or a combination of many other antioxidants to alleviate its Caspase-3 based neurotoxicity. I'm including it because it is without a doubt the most commonly used mind-altering drug on the planet, and many individuals will not consider halting consumption, although it reduces sleep quality and is therefore one of the worst drugs to consume daily, it is an excellent ergogenic to enhance exercise intensity and delay muscle aging. Please remember that Caffeine is primarily catabolic, meaning it stimulates metabolism and mitochondrial function, therefore it is best paired with either Lactic Acid Training or Cardiovascular Training, but not with High Load Strength Training, as it suppresses mTOR.

Of note, chronic daily Caffeine use will result in accelerated aging due to a concurrent decrease in sleep efficiency. Utilizing Caffeine only one or two days per week before or during exercise is ideal if you suffer from psychological issues, wherein daily caffeine abuse will undoubtedly magnify your mental deterioration through multiple mechanisms.

Interestingly, Caffeine may be able to partially counteract *antioxidant-induced mitochondrial stasis* as I call it, if administered acutely, in high dosages.
[See: Micro-Essays: Time Sensitive Caffeine Dosing: Pg. 1076]

[A] Caffeine enhances Skeletal Muscle IL-6, which explains its primary benefit to athletes who engage in high frequency training.

"<>Caffeine intake is associated with a reduced risk developing non-alcoholic fatty liver disease (NAFLD), but the underlying molecular mechanisms remain to be fully elucidated. We report here that caffeine markedly improved high fat diet-induced NAFLD in mice resulting in a 10-fold increase in circulating IL-6 levels, leading to STAT3 activation in the liver. Interestingly, the expression of IL-6 mRNA was not increased in the liver, but increased substantially in the muscles of caffeine-treated mice. <>Caffeine was found to stimulate IL-6 production in cultured myotubes but not in hepatocytes, adipocytes, or macrophages. The inhibition of p38/MAPK abrogated caffeine-induced IL-6 production in muscle cells. Caffeine failed to improve NAFLD in IL-6 and hepatocyte-specific STAT3 knockout mice, indicating that the IL-6/STAT3 pathway is vital for the hepatoprotective effects of caffeine in NAFLD. The possibility that IL-6/STAT3-mediated hepatic autophagosome induction and hepatocytic oxygen consumption are involved in the anti-NAFLD effects of caffeine cannot be excluded, based on the findings presented here. Our results reveal that caffeine ameliorates NAFLD via crosstalk between muscle IL-6 production and liver STAT3 activation."[221.0]

[B] Caffeine activates AMPK Alpha 1 Isoform, thus potentially promoting Myogenesis in low dosages, and at the very least increasing Lipolysis.

“<>Aim: Caffeine activates 5'AMP-activated protein kinase (AMPK), a signalling intermediary implicated in the regulation of glucose, lipid and energy metabolism in skeletal muscle. Skeletal muscle expresses two catalytic α subunits of AMPK, α1 and α2, but the isoform specificity of caffeine-induced AMPK activation is unclear. The aim of this study was to determine which α isoform is preferentially activated by caffeine in vitro and in vivo using rat skeletal muscle.
<>Methods: Rat epitrochlearis muscle was isolated and incubated in vitro in the absence or presence of caffeine. In another experiment, the muscle was dissected after intravenous injection of caffeine. Isoform-specific AMPK activity, the phosphorylation status of AMPKα Thr(172) and acetyl-CoA carboxylase (ACC) Ser(79) , the concentrations of ATP, phosphocreatine (PCr) and glycogen, and 3-O-methyl-d-glucose (3MG) transport activity were estimated.
<>Results: Incubation of isolated epitrochlearis muscle with 1 mm of caffeine for 15 min increased AMPKα1 activity, but not AMPKα2 activity; concentrations of ATP, PCr and glycogen were not affected. Incubation with 3 mm of caffeine activated AMPKα2 and reduced PCr and glycogen concentrations. Incubation with 1 mm of caffeine increased the phosphorylation of AMPK and ACC and enhanced 3MG transport. Intravenous injection of caffeine (5 mg kg(-1)) predominantly activated AMPKα1 and increased 3MG transport without affecting energy status.”[221]

[C] Caffeine is anti-fibrotic.

"<>Caffeine downregulated expression of type I and type III TGF-β receptors, and Smad2; and potentiated TGF-β signaling in vitro. In vivo, caffeine administration normalized body mass under hyperoxic conditions, and normalized Smad2 phosphorylation detected in lung homogenates; however, caffeine administration neither improved nor worsened lung structure in hyperoxia-exposed mice, in which postnatal lung maturation was blunted."[222]

[D] Caffeine atrophies muscle fibers.

"<>Caffeine treatment significantly reduced mTORC1 signaling, total protein synthesis and myotube diameter in a CaMKKβ/AMPK-dependent manner. Further, caffeine promoted a CaMKII-dependent increase in myostatin mRNA expression that did not significantly contribute to the caffeine-dependent reduction in protein synthesis. Our results indicate that short-term caffeine exposure significantly reduced skeletal myotube diameter by increasing autophagic flux and promoting a CaMKKβ/AMPK-dependent reduction in protein synthesis."[223]

[E] Caffeine and Nicotine permanently reduce muscle force production through interacting with the acetylcholine receptors of newly forming muscle cells (hyperplasia), which is not a worry for most.

"<>Caffeine, nicotine, or both significantly decreased agrin-induced AChR clustering during short-term and long-term exposure. Furthermore, caffeine, nicotine, or both significantly decreased spontaneous AChR clustering during long-term, but not short-term exposure. Surprisingly, caffeine and nicotine in combination did not decrease AChR clustering beyond the effect of either treatment alone. We conclude that physiologically relevant concentrations of caffeine or nicotine decrease AChR clustering. Moreover, we predict that fetuses exposed to caffeine or nicotine may be less likely to form appropriate neuromuscular synapses."[224]

[F] Caffeine activates the neuromuscular junction.

"<>The ergogenic effects of caffeine in human exercise have been shown to improve endurance and anaerobic exercise performance. Previous work has demonstrated that 70 μM caffeine (physiological maximum) can directly increase mouse extensor digitorum longus (EDL) muscle power output (PO) in sprintlike activity by 3%. Our study used the work loop technique on isolated mouse muscles to investigate whether the direct effect of 70 μM caffeine on PO differed between 1) maximally and submaximally activated muscle; 2) relatively fast (EDL) and relatively slow (soleus) muscles; and 3) caffeine concentrations. Caffeine treatment of 70 μM resulted in significant improvements in PO in maximally and submaximally activated EDL and soleus ($P < 0.03$ in all cases). For EDL, the effects of caffeine were greatest when the lowest, submaximal stimulation frequency was used ($P < 0.001$).
<>Caffeine treatments of 140, 70, and 50 μM resulted in significant improvements in acute PO for both maximally activated EDL (3%) and soleus (6%) ($P < 0.023$ in all cases); however, there was no significant difference in effect between these concentrations ($P > 0.420$ in all cases). Therefore, the ergogenic effects of caffeine on PO were higher in muscles with a slower fiber type ($P < 0.001$). Treatment with 35 μM caffeine failed to elicit any improvement in PO in either muscle ($P > 0.72$ in both cases). Caffeine concentrations below the physiological maximum can directly potentiate skeletal muscle PO. This caffeine-induced increase in force could provide similar benefit across a range of exercise intensities, with greater gains likely in activities powered by slower muscle fiber type."[225]

[G] Caffeine destroys blood vessels by way of increased Caspase-3 activity.

"<>Numerous studies have shown that adenosine or adenosine agonists can stimulate angiogenesis. However, the effect of caffeine (a known adenosine receptor antagonist) on angiogenesis has not been previously studied. Accordingly, this study was undertaken to examine the effect of caffeine on angiogenesis and to clarify the mechanism involved. Chick chorioallantoic membrane assays were used to investigate the effect of caffeine on angiogenesis and proliferation assays using human umbilical vein endothelial cells (HUVECs), were used to study its effects on specific aspects of angiogenesis. The expressions of caspase-3 and Bcl-2 were examined by western blotting, immunofluorescence staining was used to identify HUVEC morphological changes, and

fluorescence activated cell sorting (FACS) and DAPI staining were used to detect HUVEC apoptosis.
<>Caffeine was found to inhibit blood vessel formation dose-dependently and to inhibit the proliferation of HUVECs time- and dose-dependently. FACS analysis and DAPI staining showed that inhibitory effect of caffeine on HUVEC proliferation was the result of apoptosis and the up-regulation of thrombospondin-1 (TSP-1). <>Furthermore, TSP-1 levels were down-regulated by NECA but were unaffected by CGS21680, indicating that caffeine regulated TSP-1 expression via adenosine A2B receptor. In addition, caffeine up-regulated caspase-3 and down-regulated Bcl-2 at the protein level. These results suggest that the inhibitory effect of caffeine on angiogenesis is associated, at least in part, with its induction of endothelial cell apoptosis, probably mediated by a caspase-3 dependent mechanism."[226]

[H] Caffeine when combined with Nicotine significantly promotes memory acquisition, motor memory, and decreases body weight. In my subjective experience these two chemicals plateau in combinatory effect at around 4-days of chronic use, paralleling the desensitization of the Nicotinic Acetylcholine Receptors, with a beneficial cognitive effect persisting for a two-four weeks, followed by neurotoxicity developing from a loss in slow-wave sleep and excess ROS generation.

"<>There is a greater prevalence of cigarette smoking among caffeine dependent individuals. This study therefore sought to assess the effect of nicotine and/or caffeine on some key biochemical indices and neurobehavioural parameters associated with brain function in male mice. Forty male BALB/c mice were divided into 4 groups of 10 animals each; Group A serve as the control and received normal saline (s.c), Group B received 2mg/kg body weight of nicotine (s.c), Group C received 2mg/kg body weight of caffeine (s.c) and Group D received 2mg/kg of nicotine and 2mg/kg of caffeine (s.c). The experiment lasted for 21 days, and then the animals were subjected to behavioral test. Thereafter the animals were sacrificed and their brain isolated for the determination of endothelial nitric oxide (NO) level, acetylcholinesterase (AChE), arginase (Arg) and adenosine deaminase (ADA) activities; as well as some antioxidant indices.
<>Administration of nicotine or caffeine caused a significant ($P<0.05$) inhibition on AChE, ADA and Arg activities as well as a significant increase in NO level when compared with the control. However, it was observed from this study that nicotine enhances caffeine cognitive properties through a significant increase in non-spatial working memory whereas; it was otherwise on the spatial working memory and motor coordination.
<>Therefore, we can suggest from our present study that caffeine enhances the effect of nicotine either synergistically or additively on memory and motor function and some key biochemical indices associated with brain function in male mice."[227]

[I] Caffeine may be toxic to muscle cells, but only when myofibers are exposed to high concentrations of it for extended periods of time. This does not mean that Caffeine does

not negatively impact muscle growth, it clearly does, but it surely does not destroy muscle tissue, unless you're megadosing (600mg+/day).

"<>Caffeine is a widely consumed stimulant that has previously been shown to promote cytotoxic stress and even cell death in numerous mammalian cell lines. Thus far there is little information available regarding the toxicity of caffeine in skeletal muscle cells. Our preliminary data revealed that treating C2C12 myotubes with 5 mM caffeine for 6 h increased nuclear fragmentation and reduced basal and maximal oxygen consumption rate (OCR) in skeletal myotubes. The purpose of this study was to further elucidate the pathways by which caffeine increased cell death and reduced mitochondrial respiration. We specifically examined the role of c-Jun N-terminal kinase (JNK), which has previously been shown to simultaneously increase caspase-dependent cell death and reduce mitochondrial respiration in other mammalian cell lines.
<>We found that caffeine promoted a dose-dependent increase in cell death in multinucleated myotubes but did not in mononucleated myoblasts. The addition of 10 μM Z-DEVD-FMK, a specific inhibitor of executioner caspases, completely inhibited caffeine-dependent cell death. Further, the addition of 400 μM dantrolene, a specific ryanodine receptor (RYR) inhibitor, prevented the caffeine-dependent increase in cell death and the reduction in basal and maximal OCR. We also discovered that caffeine treatment significantly increased the phosphorylation of JNK and that the addition of 30 μM SP600125 (JNKi), a specific JNK inhibitor, partially attenuated caffeine-induced cell death without preventing the caffeine-dependent reduction in basal and maximal OCR.
<>Our results suggest that JNK partially mediates the increase in caspase-dependent cell death but does not contribute to reduced mitochondrial respiration in caffeine-treated skeletal muscle cells. We conclude that caffeine increased cell death and reduced mitochondrial respiration in a calcium-dependent manner by activating the RYR and promoting reticular calcium release."[228]

[J] Caffeine breaks down amyloid plaques.

"<>We have recently shown that Alzheimer's disease (AD) transgenic mice given a moderate level of caffeine intake (the human equivalent of 5 cups of coffee per day) are protected from development of otherwise certain cognitive impairment and have decreased hippocampal amyloid-beta (Abeta) levels due to suppression of both beta-secretase (BACE1) and presenilin 1 (PS1)/gamma-secretase expression. To determine if caffeine intake can have beneficial effects in "aged" APPsw mice already demonstrating cognitive impairment, we administered caffeine in the drinking water of 18-19 month old APPsw mice that were impaired in working memory.
<>At 4-5 weeks into caffeine treatment, those impaired transgenic mice given caffeine (Tg/Caff) exhibited vastly superior working memory compared to the continuing impairment of control transgenic mice. In addition, Tg/Caff mice had substantially reduced Abeta deposition in hippocampus (decrease 40%) and entorhinal cortex

(decrease 46%), as well as correlated decreases in brain soluble Abeta levels. Mechanistically, evidence is provided that caffeine suppression of BACE1 involves the cRaf-1/NFkappaB pathway.
<>We also determined that caffeine concentrations within human physiological range effectively reduce active and total glycogen synthase kinase 3 levels in SweAPP N2a cells. Even with pre-existing and substantial Abeta burden, aged APPsw mice exhibited memory restoration and reversal of AD pathology, suggesting a treatment potential of caffeine in cases of established AD."[229]

[K] Caffeine promotes skeletal muscle autophagy. Therefore, caffeine will delay muscle aging.

"<>Caffeine is a highly catabolic dietary stimulant. High caffeine concentrations (1-10 mM) have previously been shown to inhibit protein synthesis and increase protein degradation in various mammalian cell lines. The purpose of this study was to examine the effect of short-term caffeine exposure on cell signaling pathways that regulate protein metabolism in mammalian skeletal muscle cells. Fully differentiated C2C12 skeletal myotubes either received vehicle (DMSO) or 5 mM caffeine for 6 h. <>Our analysis revealed that caffeine promoted a 40% increase in autolysosome formation and a 25% increase in autophagic flux. In contrast, caffeine treatment did not significantly increase the expression of the skeletal muscle specific ubiquitin ligases MAFbx and MuRF1 or 20S proteasome activity.
<>Caffeine treatment significantly reduced mTORC1 signaling, total protein synthesis and myotube diameter in a CaMKKβ/AMPK-dependent manner. Further, caffeine promoted a CaMKII-dependent increase in myostatin mRNA expression that did not significantly contribute to the caffeine-dependent reduction in protein synthesis. Our results indicate that short-term caffeine exposure significantly reduced skeletal myotube diameter by increasing autophagic flux and promoting a CaMKKβ/AMPK-dependent reduction in protein synthesis."[229.1]

Coffee

[L] The effect of Light, Moderate, or Dark Roast Coffee on Cytokines:
Dark Roast: Enhances: IL-10, IL-1, TNF-a. Suppresses: COX2.
Light/Moderate Roast: Inconsequential effects.[230]

[L1] Dark Roast Coffee appears to have a higher concentration of the lipolytic compound N-methylpyridinum, which promotes thermogenesis.

"Coffee consumption sometimes is associated with symptoms of stomach discomfort. This work aimed to elucidate whether two coffee beverages, containing similar amounts of caffeine, but differing in their concentrations of (β) N-alkanoyl-5-hydroxytryptamides (C5HTs), chlorogenic acids (CGAs), trigonelline, and N-methylpyridinium (N-MP) have

different effects on gastric acid secretion in healthy volunteers. The intragastric pH after administration of bicarbonate with/without 200 mL of a coffee beverage prepared from a market blend or dark roast blend was analyzed in nine healthy volunteers. Coffee beverages were analyzed for their contents of C5HT, N-MP, trigonelline, CGAs, and caffeine using HPLC-DAD and HPLC-MS/MS. Chemical analysis revealed higher concentrations of N-MP for the dark brown blend (87 mg/L) compared to the market blend coffee (29 mg/L), whereas concentrations of C5HT (0.012 versus 0.343 mg/L), CGAs (323 versus 1126 mg/L), and trigonelline (119 versus 343 mg/L) were lower, and caffeine concentrations were similar (607 versus 674 mg/mL).”[231]

[L2] “<>N-Methylpyridinium (NMP) is a thermal degradation product of trigonelline formed upon coffee roasting and hypothesized to exert several health benefits in humans. Since for trigonelline evidence for hypoglycemic effects exists, we examined whether NMP also affects mechanisms of glucose utilization and cellular energy formation. For this purpose, the impact of trigonelline and NMP on respiratory activity, extracellular acidification, cellular adenosine nucleotides, energy supply from fatty acids and glucose as well as thermogenesis in HepG2 cells was analyzed. <>A 24 hour incubation with nanomolar concentrations of NMP enhanced oxygen consumption rates, resulting in increased ATP levels. Glucose was identified as the prevalent energy substrate as its uptake was augmented up to 18.1% ± 7.44% by NMP at 0.09 μM, whereas the uptake of fatty acids decreased upon NMP treatment. Cellular glucose uptake was also stimulated by trigonelline administration; however, a shift to the anaerobic energy production pathway was monitored. Both pyridine derivatives induced thermogenesis, although trigonelline presumably promoted proton leaks, while NMP increased the concentration of the uncoupling protein-2.
<>We provide evidence that both compounds appear to stimulate cellular energy metabolism in HepG2 cells. Human intervention studies are warranted to ensure these effects in vivo.”[232]

[L3] The common Swiss Water Method of coffee decaffeination results in toxic Aluminum accumulation in post-processed coffee, thus making CO2 decaffeinated coffee the better choice.

“<>The effect of new coffee brewing, coffee capsules, on the antioxidant activity (ORAC and ABTS), total phenolic content, chlorogenic acid, caffeine, and melanoidin concentration was assessed and compared with the conventional coffeemakers (filter, mocha, and expresso). In addition, the aluminum content was also analyzed to investigate the potential migration of this metal from the capsule to the beverages. The capsule method showed the lowest values of antioxidant capacity and total phenolic content. Capsule coffeemaker had the lowest extraction yield of the main coffee antioxidants (chlorogenic acid and melanoidins).

<>On average, the highest amount of aluminum was obtained in decaffeinated coffees. Moreover, despite the fact that the coffee is considered to be a poor source of aluminum for humans, when the sample is decaffeinated, especially by Swiss Water® method and prepared by capsule machine, its aluminum content notably increases. The data collected provide useful insights for the selection of the type of coffee beverage with the major content of bioactive compounds and the minor content of harmful components for health."[233.1]

[M] Coffee roasting results in the formation of chemical compounds called Melanoidins which form during the Maillard Reaction, which is when amino acids, sugars, & heat cause a chemical reaction to occur. Melanoidins give bread and coffee the visual appearance of the color brown.

Importantly, Melanoidins were found to be intestinal antioxidants, and promote the growth of beneficial bacteria.

"<>Melanoidins are an important component of the human diet (average consumption 10 g/day), which escape gastrointestinal digestion and are fermented by the gut microbiota. In this study melanoidins from different food sources (coffee, bread, beer, balsamic vinegar, sweet wine, biscuit, chocolate, and breakfast cereals) were submitted to an in vitro digestion and fermentation process, and their bioactivity was assessed.
<>Some melanoidins were extensively used by gut microbes, increasing production of short chain fatty acids (mainly acetate and lactate) and favoring growth of the beneficial genera Bifidobacterium (bread crust, pilsner and black beers, chocolate and sweet wine melanoidins) and Faecalibacterium (biscuit melanoidins). Quantification of individual phenolic compounds after in vitro fermentation allowed their identification as microbial metabolites or phenolics released from the melanoidins backbone (specially pyrogallol, 2-(3,4-dihydroxyphenyl)acetic and 3-(3,4-dihydroxyphenyl)propionic acids).
<>Our results also showed that antioxidant capacity of melanoidins is affected by gut microbiota fermentation."[233.2]

Camellia Sinensis Teas

White & Matcha Teas are the least processed, and freshest teas, followed by Green Tea's which are minimally processed, and finally Oolong, Black, & Dark Teas are oxidized purposefully to far greater extents to change their chemistry and flavor profiles. All Camellia Sinensis Teas are good for the body and brain when consumed, but traditional and inexpensive Green Tea will always be the most powerful all-around antioxidant.

[N] Traditional Tea (Camellia Sinensis) contains numerous heavy metals. Black Tea appears to contain the highest amount of Aluminum & Chromium, whereas Herbal Tea's contain higher amounts of other heavy metals, such as Arsenic, and Lead.

"<>Food and beverage consumption is an important route for human exposure to metals. Traditional tea (Camellia sinensis) is a widely-consumed beverage, which may contain toxic metals. This study determined total and infusion concentrations of 5 metals including Al, As, Cd, Cr, and Pb in 47 traditional and herbal teas from 13 countries and assessed their potential risks to human health.
<>The data showed that herbal teas exhibited higher As (0.26mgkg-1), Cd (0.19mgkg-1) and Pb (2.32mgkg-1) than traditional teas. Black tea from India had high Cr at 31mgkg-1 while white tea from China had low Cr at 0.39mgkg-1. Arsenic, Cd and Pb did not exceed the WHO limit for medicinal plants excluding one herbal tea with 1.1mgkg-1 As and 26.4mgkg-1 Pb.
<>However, Cr in 47% herbal teas and 73% traditional teas exceeded the Canada limit of 2mgkg-1. Metal concentrations in tea infusions were below the MCL for drinking water except for Al. Total Al and its infusion was lower in herbal teas (47-1745mgkg-1 and 0.09-3.95mgL-1) than traditional teas (50.3-2517mgkg-1 and 0.02-7.51mgL-1), with 0.9-22% and 4-49% of the Al being soluble in infusion.
<>The Al concentrations in infusion in all black tea and 83, 75 and 25% of the green, oolong and herbal teas exceeded the secondary MCL for drinking water at 0.2mgL-1. However, the weekly intake of Al from drinking tea (0.001-0.39 and 0.003-0.56mgkg-1 for children and adults) was lower than the provisional tolerable weekly intake for Al at 1.0mgkg-1.
<>Our data showed that it is important to consider metal intake from tea consumptions, especially for Cr and Al in heavy tea drinkers."
"The benefits of drinking tea are multiple, contributing to daily intake of essential minerals and benefit overall human health. However, teas may also contain toxic metals including Al (Table 2), and As, Cd, Cr and Pb (Table 3). The mean Al content in herbal teas was 548 mg kg−1, which was lower than 885, 1089 and 1655 mg kg−1 in green, oolong and black teas."[233.3]

Black Tea

Camellia Sinensis leaves experience a chemical reaction during the fermentation and oxidation processes that convert Green to Black Tea, wherein the Green Tea catechins (polyphenols) breakdown during processing into other polyphenolic molecules, called Theaflavins, which have similar but distinctly different effects on the body.

[N1] Black Tea chemical components (likely Theaflavins) promote Glutathione production and cause a reduction in training-induced Cortisol secretion.

"<>Background: Muscle soreness and decreased performance often follow a bout of high-intensity exercise. By reducing these effects, an athlete can train more frequently and increase long-term performance. The purpose of this study is to examine whether a high-potency, black tea extract (BTE) alters the delayed onset muscle soreness (DOMS), oxidative stress, inflammation, and cortisol (CORT) responses to high-intensity anaerobic exercise.

<>Methods: College-age males (N = 18) with 1+ yrs of weight training experience completed a double-blind, placebo-controlled, crossover study. Subjects consumed the BTE (1,760 mg BTE.d-1) or placebo (PLA) for 9 days. Each subject completed two testing sessions (T1 & T2), which occurred on day 7 of the intervention. T1 & T2 consisted of a 30 s Wingate Test plus eight 10 s intervals. Blood samples were obtained before, 0, 30 & 60 min following the interval sessions and were used to analyze the total to oxidized glutathione ratio (GSH:GSSG), 8-isoprostane (8-iso), CORT, and interleukin 6 (IL-6) secretion. DOMS was recorded at 24 & 48 h post-test using a visual analog scale while BTE or PLA continued to be administered. Significance was set at $P < 0.05$.
<>Results: Compared to PLA, BTE produced significantly higher average peak power ($P = 0.013$) and higher average mean power ($P = 0.067$) across nine WAnT intervals. BTE produced significantly lower DOMS compared to PLA at 24 h post test ($P < 0.001$) and 48 h post test ($P < 0.001$). Compared to PLA, BTE had a slightly higher GSH:GSSG ratio at baseline which became significantly higher at 30 and 60 min post test ($P < 0.002$). AUC analysis revealed BTE to elicit significantly lower GSSG secretion ($P = 0.009$), significantly higher GSH:GSSG ratio ($P = 0.001$), and lower CORT secretion ($P = 0.078$) than PLA. AUC analysis did not reveal a significant difference in total IL-6 response ($P = 0.145$) between conditions.
<>Conclusions: Consumption of theaflavin-enriched black tea extract led to improved recovery and a reduction in oxidative stress and DOMS responses to acute anaerobic intervals. An improved rate of recovery can benefit all individuals engaging in high intensity, anaerobic exercise as it facilitates increased frequency of exercise."[234]

[N2] Black Tea, to a similar degree to Green Tea, vasodilates blood vessels.

"<>Epidemiological studies suggest that consumption of tea is associated with beneficial cardiovascular effects. Since different types of tea are consumed throughout the world, a question of much interest is whether green tea is superior to black tea in terms of cardiovascular protection. We therefore compared the effects of green and black tea on nitric oxide (NO) production and vasodilation and elucidated the tea compounds involved. We chose a highly fermented black tea and determined concentrations of individual tea compounds in both green and black tea of the same type (Assam).
<>The fermented black tea was almost devoid of catechins. However, both teas stimulated eNOS activity and phosphorylation in bovine aortic endothelial cells (BAEC) as well as vasorelaxation in rat aortic rings to a similar extent. In green tea, only epigallocatechin-3-gallate (EGCG) resulted in pronounced NO production and NO-dependent vasorelaxation in aortic rings. During tea processing to produce black tea, the catechins are converted to theaflavins and thearubigins. Individual black tea theaflavins showed a higher potency than EGCG in NO production and vasorelaxation.
<>The thearubigins in black tea are highly efficient stimulators of vasodilation and NO production. Green and black tea compounds induced comparable phosphorylation of eNOS and upstream signalling kinases. Whereas stimulation of eNOS activity by EGCG was only slightly affected by pretreatment of cells with various ROS scavengers,

TF3(theaflavin-3',3-digallate)-induced eNOS activity was partially inhibited by PEG-catalase.
<>These results implicate that highly fermented black tea is equally potent as green tea in promoting beneficial endothelial effects. Theaflavins and thearubigins predominantly counterbalance the lack of catechins in black tea. The findings may underline the contribution of black tea consumption in prevention of cardiovascular diseases."[234.1]

[N3] Black Tea, through its concentration of Theaflavins, increases Dopamine production in the prefrontal cortex.

"<>Epidemiological investigations have reported that the habit of drinking tea reduces the risk of developing a mental disorder, including anxiety disorder and depression. Theaflavins, black tea polyphenols, show antibacterial and anti-oxidative effects, but their effects on brain function, especially mental condition, have not been elucidated. The present study demonstrated that theaflavins increased dopamine (DA) turnover in the frontal cortex and showed an anxiolytic effect in mice. Theaflavin consumption increased the time spent by mice in the open arms of an elevated plus maze test. Theaflavin administration increased the levels of 3,4-dihydroxyphenylacetic acid (DOPAC) and the ratios of DOPAC/DA and (DOPAC+homovanillic acids)/DA indicating DA turnover, in the frontal cortex. <>These results suggest that the consumption of theaflavins induced anxiolytic effects via activation of the dopaminergic system in the frontal cortex, which support the findings of previous epidemiological studies. Theaflavins in black tea may be helpful to reduce anxiety in daily life."[234.2]

[N4] Black Tea polyphenols promote slow twitch fiber recovery after atrophy.

"<>Previously, we reported that polyphenol-rich fraction (named E80) promotes skeletal muscle hypertrophy induced by functional overload in mice. This study indicates that E80 has potential for affecting skeletal muscle mass. Then, we evaluate the effect of E80 on atrophic and recovery conditions of skeletal muscle in mice. Hindlimb suspension (unloading) and relanding (reloading) are used extensively to observe disuse muscle atrophy and subsequent muscle mass recovery from atrophy. Eight-week old C57BL/6 mice were fed either a normal diet or a diet containing 0.5% E80 for two weeks under conditions of hindlimb suspension and a subsequent 5 or 10 days of reloading.
<>We found that E80 administration did not prevent atrophy during hindlimb suspension, but promoted recovery of slow-twitch (soleus) muscle mass from atrophy induced by hindlimb suspension. After five days of reloading, we discovered that phosphorylation of the Akt/mammalian target of rapamycin (mTOR) pathway proteins, such as Akt and P70 ribosomal protein S6 kinase (S6K), was activated in the muscle. Therefore, E80 administration accelerated mTOR signal and increased protein synthesis in the reloaded soleus muscle."[234.2.1]

[See: Neuromuscular Junction Supplementation & Modalities: Theaflavins]

Green Tea & Matcha

If you prefer drinking Green Tea, keep in mind that EGCg and other catechins have an *astringent* (unpleasant) flavor[234.3]. Matcha Green teas that are smooth and subtle on the palate may be high in L-Theanine but are not good sources of polyphenols such as EGCg. Generic and inexpensive Green Teas are the greatest source of EGCg in grocery stores. Although the more expensive and higher quality grade of Matcha Green Tea, Ceremonial grade Matcha, is a great source of L-Theanine, it is relatively devoid of polyphenols, and it seems rather unintelligent to supplement traditional forms of Camellia Sinensis tea for one with such a lack of phytochemical makeup, and such a high price tag, especially when L-Theanine can be purchased as a standalone product, and easily added to any drink or tea as a simple way to create the sought after L-Theanine-induced "Umami" flavor, and attain its nootropic benefits.

[See: Anti-Inflammation Cycle Supplementation: EGCg]

White Tea

[N4] White Tea contains similar levels of Catechins (polyphenols) to Green Tea but may be missing, likely in concentration, the non-catechin antioxidants present in Green Tea, making Green Tea a better antioxidant supplement for the sick or elderly.

"<>Recent investigations have associated white teas with anti-carcinogenic, immune-boosting, and antioxidative properties that may impact human health in a manner comparable to green teas. An in-depth chemical analysis of white tea types was conducted to quantify polyphenols and antioxidant potential of 8 commercially available white teas, and compare them to green tea. Extraction and HPLC protocols were optimized and validated for the quantification of 9 phenolic and 3 methylxanthine compounds to examine inter- and intra-variation in white and green tea types and subtypes. A sampling strategy was devised to assess various subtypes procured from different commercial sources.
<>Variation in antioxidant activity and total phenolic content (TPC) of both tea types was further assessed by the 1-1-diphenyl-2-picrylhydrazyl (DPPH) and Folin-Ciocalteau (F-C) assays, respectively.
<>Total catechin content (TCC) for white teas ranged widely from 14.40 to 369.60 mg/g of dry plant material for water extracts and 47.16 to 163.94 mg/g for methanol extracts. TCC for green teas also ranged more than 10-fold, from 21.38 to 228.20 mg/g of dry plant material for water extracts and 32.23 to 141.24 mg/g for methanol extracts. These findings indicate that statements suggesting a hierarchical order of catechin content among tea types are inconclusive and should be made with attention to a sampling strategy that specifies the tea subtype and its source.
<>Certain white teas have comparable quantities of total catechins to some green teas, but lesser antioxidant capacity, suggesting that white teas have fewer non-catechin antioxidants present.

<>Practical Application: In this investigation white and green teas were extracted in ways that mimic common tea preparation practices, and their chemical profiles were determined using validated analytical chemistry methods. The results suggest certain green and white tea types have comparable levels of catechins with potential health promoting qualities. Specifically, the polyphenolic content of green teas was found to be similar to certain white tea varieties, which makes the latter tea type a potential substitute for people interested in consuming polyphenols for health reasons. Moreover, this study is among the first to demonstrate the effect subtype sampling, source of procurement, cultivation, and processing practices have on the final white tea product, as such analysis has previously been mostly carried out on green teas."[234.4]

Dark Tea

[N5] The respective phytochemicals within oxidized and fermented Camellia Sinensis Teas, most especially "Dark Teas" which are fermented twice or for longer periods of time, e.g. Pu'er Tea, possess greater abilities to inhibit amyloid formation, although this does not discount the anti-amyloidogenic benefits of EGCg (Green Tea) as you will soon learn. Pu'er Tea contains the polyphenols Theabrownins, which are the oxidization-induced breakdown products of theaflavins and thearubigins, the primarily polyphenols found in black teas. The problem with Dark Tea's is that they contain a very high concentration of caffeine.

"<>White tea belongs to light-fermented tea, and dark tea belongs to post-fermented tea. The longer the two types of tea are stored, the better the efficacy and flavor quality. During the storage process, the components of tea are transformed, and the active components such as tea pigment, organic acid, and tea polysaccharide are gradually increased, and the quality and efficacy of tea are gradually improved. The results indicate that dark tea has significant antioxidant activity in vivo, and the antioxidant activity of Liupao dark tea is even better than that of some green tea. These results are consistent with our results.
<>The latest research shows that catechins and theanine gradually condense during the fermentation process of white tea and dark tea to form a kind of flavoalkaloids products condensed at C8 position. Efficacy and mechanism evaluations show that the C8 condensed flavoalkaloids have significant antioxidant and inhibitory activities on the formation of amyloid in premature aging SAMP8 mice. The results show that aged white tea, black tea, and dark tea have lower catechin content than green tea, but still have significant inhibitory activity on amyloid formation.
<>Our study results indicated that different tea types have a significant inhibitory effect on the formation of β-amyloid mediated by age-related lipid metabolism disorders, and the in vivo activity of fully fermented teas was better than that of green tea."[234.5]

[N6] Pu'er Tea that has been aged contains a higher level of caffeine then other teas. "Pu-erh tea is a popular beverage in southwestern China and South Asian countries. To explain the differences of aged pu-erh tea and ripened pu-erh tea, the chemical

constituents of these teas were identified by HPLC-DAD-ESI-MS(n). In addition, HPLC was used to determine the contents of the major polyphenols, gallic acid, caffeine, and theobromine, in various types of teas. These results showed that the majority of chemical constituents in ripened pu-erh tea and aged pu-erh tea were similar, but the contents of catechins and gallic acid presented significant differences between these two teas. After fermentation by microorganism, the levels of catechins in ripened pu-erh tea were decreased, but the contents of gallic acid and caffeine were conversely elevated compared with aged pu-erh tea."[234.6]

CAFFEINE RESEARCH ADJUNCT

[O] Caffeine promotes memory by way of Neuropeptide S, a noradrenergic peptide.

"<>Caffeine has marked effects on sleep, arousal and food intake. However, the neuronal mechanisms underlying these actions are not fully understood. Neuropeptide S (NPS) is a recently discovered neuropeptide regulating both sleep and feeding. Here, we examined the effect of acute and chronic caffeine treatment on the expression of neuropeptide S and its receptor (NPS-R) in the hypothalamus and brainstem of rats by using real-time PCR. Our results showed that acute caffeine treatment induces a marked decrease in the mRNA levels of NPS in the brainstem, whilst the expression levels NPS-R are increased in both hypothalamus and brainstem after caffeine treatment. The timing of both processes differs, with acute treatment affecting brainstem NPS-R expression and chronic treatment affecting hypothalamic NPS-R expression. Overall, these data suggest a possible role for the NPS system in mediating some of the behavioral effects of caffeine."[235]

[O2] "<>Neuropeptide S (NPS) has been shown to promote arousal and anxiolytic-like effects, as well as facilitation of fear extinction. In rodents, NPS receptors (NPSR) are prominently expressed in brain structures involved in learning and memory. Here, we investigate whether exogenous or endogenous NPS signaling can modulate acquisition, consolidation, or recall of emotional, spatial, and contextual memory traces, using two common behavioral paradigms, inhibitory avoidance (IA) and novel object recognition.
<>In the IA paradigm, immediate and delayed post-training central NPS administration dose dependently enhanced memory retention in mice, indicating that NPS may act during the consolidation phase to enhance long-term memory. In contrast, pre-training or pre-test NPS injections were ineffective, suggesting that NPS had no effect on IA memory acquisition or recall. Peripheral administration of a synthetic NPSR antagonist attenuated NPS-induced IA memory enhancement, showing pharmacological specificity. NPS also enhanced hippocampal-dependent non-aversive memory in the novel object recognition task.
<>In contrast, NPSR knockout mice displayed deficits in IA memory, novel object recognition, and novel place or context recognition, suggesting that activity of the endogenous NPS system is required for memory formation. Blockade of adrenergic signaling by propranolol attenuated NPS-induced memory enhancement in the IA task,

indicating involvement of central noradrenergic systems. These results provide evidence for a facilitatory role of NPS in long-term memory, independent of memory content, possibly by acting as a salience signal or as an arousal-promoting factor."[236]

[P] Caffeine prevents Sleep Deprivation-induced CREB/bDNF suppression.

"<>It is well known that caffeine and sleep deprivation have opposing effects on learning and memory; therefore, this study was undertaken to determine the effects of chronic (4wks) caffeine treatment (0.3g/l in drinking water) on long-term memory deficit associated with 24h sleep deprivation. Animals were sleep deprived using the modified multiple platform method.
<>The results showed that chronic caffeine treatment prevented the impairment of long-term memory as measured by performance in the radial arm water maze task and normalized L-LTP in area CA1 of the hippocampi of sleep-deprived anesthetized rats. Sleep deprivation prevents the high frequency stimulation-induced increases in the levels of phosphorylated-cAMP response element binding protein (P-CREB) and brain-derived neurotrophic factor (BDNF) seen during the expression of late phase long-term potentiation (L-LTP). However, chronic caffeine treatment prevented the effect of sleep-deprivation on the stimulated levels of P-CREB and BDNF.
<>The results suggest that chronic caffeine treatment may protect the sleep-deprived brain probably by preserving the levels of P-CREB and BDNF."[237]

[Q] Caffeine reduces slow wave sleep, the most important type of sleep.

"Caffeine is the most widely consumed psychoactive substance in the world. It is readily available in coffee and other foods and beverages, and is used to mitigate sleepiness, enhance performance, and treat apnea in premature infants. This review systematically explores evidence from epidemiological studies and randomized controlled trials as to whether coffee and caffeine have deleterious effects on sleep. Caffeine typically prolonged sleep latency, reduced total sleep time and sleep efficiency, and worsened perceived sleep quality. Slow-wave sleep and electroencephalographic (EEG) slow-wave activity were typically reduced, whereas stage-1, wakefulness, and arousals were increased. Dose- and timing-response relationships were established. The sleep of older adults may be more sensitive to caffeine compared to younger adults."[238]

[R] Chronic caffeine use results in tolerance to its performance enhancing effects. Athletes should then withdraw from it (72 hours) before a competition and reintroduce it pre/intra-competition.

"<>This study examined effects of 4 weeks of caffeine supplementation on endurance performance. Eighteen low-habitual caffeine consumers (<75 mg · day-1) were randomly assigned to ingest caffeine (1.5-3.0 mg · kg-1day-1; titrated) or placebo for 28 days. Groups were matched for age, body mass, V̇O2peak and Wmax ($P > 0.05$). Before

supplementation, all participants completed one V̇O2peak test, one practice trial and 2 experimental trials (acute 3 mg · kg-1 caffeine [precaf] and placebo [testpla]). During the supplementation period a second V̇O2peak test was completed on day 21 before a final, acute 3 mg · kg-1 caffeine trial (postcaf) on day 29. Trials consisted of 60 min cycle exercise at 60% V̇O2peak followed by a 30 min performance task.
<>All participants produced more external work during the precaf trial than testpla, with increases in the caffeine (383.3 ± 75 kJ vs. 344.9 ± 80.3 kJ; Cohen's d effect size [ES] = 0.49; P = 0.001) and placebo (354.5 ± 55.2 kJ vs. 333.1 ± 56.4 kJ; ES = 0.38; P = 0.004) supplementation group, respectively. This performance benefit was no longer apparent after 4 weeks of caffeine supplementation (precaf: 383.3 ± 75.0 kJ vs. postcaf: 358.0 ± 89.8 kJ; ES = 0.31; P = 0.025), but was retained in the placebo group (precaf: 354.5 ± 55.2 kJ vs. postcaf: 351.8 ± 49.4 kJ; ES = 0.05; P > 0.05).
<>Circulating caffeine, hormonal concentrations and substrate oxidation did not differ between groups (all P > 0.05). Chronic ingestion of a low dose of caffeine develops tolerance in low-caffeine consumers. Therefore, individuals with low-habitual intakes should refrain from chronic caffeine supplementation to maximise performance benefits from acute caffeine ingestion."[238.0]

[S] Caffeine magnifies alcohol withdrawal-induced neurotoxicity, and this effect is much greater in female brains.

"<>Aims: Caffeine is a central nervous system stimulant that produces its primary effects via antagonism of the A1 and A2A adenosine receptor subtypes. Previous work demonstrated a sex difference in neurotoxicity produced by specific adenosine A1 receptor antagonism during ethanol withdrawal (EWD) in vitro that was attributable to effects downstream of A1 receptors at NMDA receptors. The current studies were designed to examine the effect of non-specific adenosine receptor antagonism with caffeine during ethanol withdrawal on hippocampal toxicity in cultures derived from male and female rats.
<>Methods: At 5 days in vitro (DIV), half of the male and female organotypic hippocampal slice cultures were exposed to 50 mM ethanol (EtOH) in culture media for 10 days before exposure to caffeine (5, 20 and 100 μM) for the duration of a 24 h EWD period. In keeping with this timeline, the remaining ethanol-naïve cultures were given media changes at 10 and 15 DIV and exposed to caffeine (5, 20 and 100 μM) for 24 h at 15 DIV. Cytotoxicity was assessed by fluorescent microscopy and quantification of propidium iodide (PI) uptake in the pyramidal cell layers of the CA1 and CA3 regions and the granule cell layer of the dentate gyrus (DG). A two-way (sex × treatment) ANOVA was conducted within each hippocampal region.
<>Results: Twenty-four-hour withdrawal from 10-day exposure to 50 mM ethanol did not produce increased PI uptake in any hippocampal region. Caffeine exposure (5, 20 and 100 μM) in ethanol-naïve cultures did not produce toxicity in the DG or CA1 region, but

20 μM caffeine produced modest toxicity in the CA3 region. Exposure to 20 μM caffeine during EWD produced cytotoxicity in all hippocampal regions, though toxicity was sex-dependent in the DG and CA1 region. In the DG, both 5 and 20 μM caffeine produced significantly greater PI uptake in ethanol-exposed female cultures compared to ethanol-naïve female cultures and all male cultures. Similarly, 20 μM caffeine caused markedly greater toxicity in female cultures as compared to male cultures in the CA1 region.
<>Conclusions: Twenty-four-hour exposure to caffeine during EWD produced significant toxicity in the pyramidal cell layer of the CA3 region in male and female cultures, though toxicity in the granule cell layer of the DG and pyramidal cell layer of the CA1 region was observed only in female cultures. Greater sensitivity of the female slice cultures to toxicity upon caffeine exposure after prolonged ethanol exposure is consistent with previous studies of effects of a specific A1 receptor antagonism during EWD on toxicity and indicate that this effect is independent of the hormonal milieu.
<>Together, these data suggest that the A1 receptor subtype is predominant in mediating caffeine's neurotoxic effects during EWD. These findings demonstrate the importance of considering gender/sex when examining neuroadaptive changes in response to ethanol exposure and withdrawal."[238.00]

[T] Chronic use of Caffeine may destroy sensory hair cells through activating a glucocorticoid (corticosteroid: cortisol) pathway and suppression of HIF-1a, leading to permanent hearing loss over time. Although I believe combing Caffeine consumption with numerous antioxidants will mitigate or inhibit this "ototoxic" effect.

"<>Caffeine is being increasingly used in daily life, such as in drinks, cosmetics, and medicine. Caffeine is known as a mild stimulant of the central nervous system, which is also closely related to neurologic disease. However, it is unknown whether caffeine causes hearing loss, and there is great interest in determining the effect of caffeine in cochlear hair cells.
<>First, we explored the difference in auditory brainstem response (ABR), organ of Corti, stria vascularis, and spiral ganglion neurons between the control and caffeine-treated groups of C57BL/6 mice. RNA sequencing was conducted to profile mRNA expression differences in the cochlea of control and caffeine-treated mice. A CCK-8 assay was used to evaluate the approximate concentration of caffeine. Flow cytometry, TUNEL assay, immunocytochemistry, qRT-PCR, and Western blotting were performed to detect the effects of SGK1 in HEI-OC1 cells and basilar membranes.
<>In vivo research showed that 120 mg/ kg caffeine injection caused hearing loss by damaging the organ of Corti, stria vascularis, and spiral ganglion neurons. RNA-seq results suggested that SGK1 might play a vital role in ototoxicity. To confirm our observations in vitro, we used the HEI-OC1 cell line, a cochlear hair cell-like cell line, to investigate the role of caffeine in hearing loss.

<>The results of flow cytometry, TUNEL assay, immunocytochemistry, qRT-PCR, and Western blotting showed that caffeine caused autophagy and apoptosis via SGK1 pathway. We verified the interaction between SGK1 and HIF-1α by co-IP. To confirm the role of SGK1 and HIF-1α, GSK650394 was used as an inhibitor of SGK1 and CoCl2 was used as an inducer of HIF-1α. Western blot analysis suggested that GSK650394 and CoCl2 relieved the caffeine-induced apoptosis and autophagy. <>Together, these results indicated that caffeine induces autophagy and apoptosis in auditory hair cells via the SGK1/HIF-1α pathway, suggesting that caffeine may cause hearing loss. Additionally, our findings provided new insights into ototoxic drugs, demonstrating that SGK1 and its downstream pathways may be potential therapeutic targets for hearing research at the molecular level."[238.01]

[U] Caffeine prevents Social Defeat Stress-induced downregulation of the Cannabinoid-1 receptor, thus explaining one reason why people unconsciously seek after its use, such as those are introverted, antisocial, or suffer from genetically determined behavioral passivity (women).

"<>Caffeine, the psychoactive ingredient of coffee and of many soft drinks, is frequently abused by humans especially during stressful live events. The endocannabinoid system is involved in the central effects of many psychoactive compounds and of stress. Whether caffeine alters the cannabinoid system and interferes with stress-induced synaptic alterations is however unknown. We have studied electrophysiologically the sensitivity of cannabinoid receptors modulating synaptic transmission in the striatum of mice exposed to caffeine in their drinking solution.
<>Chronic caffeine assumption sensitized GABAergic synapses to the presynaptic effect of cannabinoid CB1 receptor stimulation by exo- and endocannabinoids. Caffeine was conversely unable to affect the sensitivity of cannabinoid receptors modulating glutamate transmission. The synaptic effects of caffeine were slowly reversible after its removal from the drinking solution.
<>Furthermore, although exposure to caffeine for only 24h did not produce measurable changes of the sensitivity of cannabinoid CB1 receptors, it was able to contrast the down-regulation of CB1 receptor-mediated responses after social defeat stress.
<>Our data suggest that the cannabinoid system is implicated in the psychoactive properties of caffeine and in the ability of caffeine to reduce the pathological consequences of stress."

[See: Unmentioned Amino Acids & Protein: Ammonia]

L-Theanine: Moderate POP

L-Theanine is a great antioxidant and nootropic, but if you use it make sure that you don't withdrawal from it by adding it to your caffeinated beverages, or water, or taking a certain dosage every two-three hours. Withdrawal from L-Theanine can cause pronounced changes in mood and memory.

[A] L-Theanine promotes LTP possibly by way of the AMPA Receptors.

"<>Theanine, γ-glutamylethylamide, is one of the major amino acid components in green tea. This study was undertaken to evaluate the effect of theanine intake on long-term potentiation (LTP) induction at hippocampal CA1 synapses and exposure to acute stress. Young rats were fed water containing 0.3% theanine after birth.
<>Key findings: Serum corticosterone level was markedly decreased by theanine intake. Because this decrease can modify synaptic plasticity, the effect of theanine intake was examined focused on CA1 LTP induction. CA1 LTP induced by a 100-Hz tetanus for 1 s was almost the same extent in hippocampal slices from theanine-administered rats, whereas that induced by a 200-Hz tetanus for 1 s was significantly attenuated. 2-Amino-5-phosphonovalerate (APV), an N-methyl-D: -aspartate (NMDA) receptor antagonist, significantly attenuated CA1 LTP induced by a 200-Hz tetanus in the control rats, but not in theanine-administered rats.
<>Interestingly, APV completely blocked CA1 LTP induced by a 100-Hz tetanus in the control rats, while scarcely blocking it in theanine-administered rats. These results indicate that theanine intake reduces NMDA receptor-dependent CA1 LTP, while increasing NMDA receptor-independent CA1 LTP.
<>Furthermore, neither 100-Hz tetanus-induced LTP nor 200-Hz tetanus-induced LTP was attenuated in theanine-administered rats after exposure to tail suspension stress, suggesting that the lack of NMDA receptor-dependent CA1 LTP by theanine intake is involved in ameliorating the attenuation of CA1 LTP after tail suspension. This study is the first to indicate that theanine intake modifies the mechanism of CA1 LTP induction."[238.02]

[B] L-Theanine promotes the transformation of fast twitch fibers to slow twitch fibers.

"<>The aim of this study was to investigate the effect of dietary L-theanine supplementation on skeletal muscle fiber type transition in mice. Our data indicated that dietary 0.15% L-theanine supplementation significantly increased the mRNA expression levels of muscle fiber type related genes (MyHC I, MyHC IIa, PGC-1α, Sirt1, Tnnt1, Tnnc1, Tnni1, MEF2C) and the protein expression levels of MyHC IIa, myoglobin, PGC-1α, Sirt1 and Troponin I-SS, but significantly decreased the mRNA and protein expression levels of MyHC IIb.
<>Dietary 0.15% L-theanine supplementation significantly increased the activities of SDH and MDH and decreased the activity of LDH. Furthermore, immunofluorescence demonstrated that dietary 0.15% L-theanine supplementation significantly increased the percentage of type I fibers, and significantly decreased the percentage of type II fibers.

<>In addition, we found that dietary 0.15% L-theanine supplementation increased the fatigue-resistant, antioxidant capacity, mitochondrial biogenesis, and function in skeletal muscle of mice. Furthermore, dietary 0.15% L-theanine supplementation significantly increased the mRNA levels of prox1, CaN and NFATc1, the protein levels of prox1, CNA and NFATc1 and the activity of CaN in GAS muscle when compared with the control group. These results indicated that dietary L-theanine supplementation promoted skeletal muscle fiber transition from type II-type I, which might be via activation of CaN and/or NFATc1 signaling pathway."[238.03]

[C] L-Theanine promotes bDNF and NGF in the brain.

"Theanine, γ-glutamylethylamide, is one of the major amino acid components in green tea. On the basis of the preventive effect of theanine intake after weaning on stress-induced impairment of recognition memory, the advantageous effect of theanine intake on recognition memory was examined in young rats, which were fed water containing 0.3% theanine for 3 weeks after weaning. The rats were subjected to object recognition test. Object recognition memory was maintained in theanine-administered rats 48 hours after the training, but not in the control rats. When in vivo dentate gyrus long-term potentiation (LTP) was induced, it was more greatly induced in theanine-administered rats than in the control rats. The levels of brain-derived neurotropic factor and nerve growth factor in the hippocampus were significantly higher in theanine-administered rats than in the control rats. The present study indicates the advantageous effect of theanine intake after weaning on recognition memory. It is likely that theanine intake is of advantage to the development of hippocampal function after weaning."[238.04]

[D] L-Theanine (being able to pass the Blood Brain Barrier) exerts strong antioxidant effects on the brain, and reduces *Caspase-3* expression following nerve injury, making it a very important antioxidant to pair with caffeine consumption.

"<>L-theanine (LT), which is a major amino acid found in green tea, was shown to alleviate Vincristine (VCR)-induced peripheral neuropathy and associated neuronal functional changes in rats. To induce peripheral neuropathy, rats were administered VCR at a dose of 100 mg/kg/day intraperitoneally on days 1-5 and 8-12, while control rats received LT at doses of 30, 100, and 300 mg/kg/day intraperitoneally for 21 days or saline solution. Electrophysiological measurements were taken to evaluate the nerve functional loss and recovery through motor and sensory nerve conduction velocities. The sciatic nerve was examined for several biomarkers, including nitric oxide (NO), malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), total calcium, IL-6, IL-10, MPO, and caspase-3.
<>The results showed that VCR caused significant hyperalgesia and allodynia in rats; decreased nerve conduction velocity; increased NO and MDA levels; and decreased GSH, SOD, CAT, and IL-10 levels. LT was found to significantly reduce VCR-induced nociceptive pain thresholds, decrease oxidative stress levels (NO, MDA), increase

antioxidative strength (GSH, SOD, CAT), and reduce neuroinflammatory activity and apoptosis markers (caspase-3).
<>LT's antioxidant, calcium homeostasis, anti-inflammatory, anti-apoptotic, and neuroprotective properties make it a potential adjuvant to conventional treatment in VCR-induced neuropathy in rats."[238.05]

[E] L-Theanine is able to partially counteract the sleep-reducing effects of caffeine. The keyword being *partially*. To incorporate this study into a protocol, an average person would need to dose 200-400mg of L-Theanine immediately before bed because the half-life of L-Theanine is far shorter than caffeine (60mins vs 300mins).

"<>L-theanine has been reported to inhibit the excitatory effects of caffeine. The present study examined the effects of L-theanine on caffeine-induced sleep disturbances in rats. Rats received the following drug pairings: saline and saline (Control), 7.5 mg/kg caffeine and saline, or 7.5 mg/kg of caffeine followed by various doses of L-theanine (22.5, 37.5, 75, or 150 mg/kg). Vigilance states were divided into: wakefulness (W), transition to slow-wave sleep (tSWS), slow-wave sleep (SWS), and rapid-eye-movement sleep (REMS).
<>Caffeine significantly increased the duration of W and decreased the duration of SWS and REMS compared to the Control. Although L-theanine failed to reverse the caffeine-induced W increase, at 22.5 and 37.5 mg/kg (but not at 75 and 150 mg/kg), it significantly reversed caffeine-induced decreases in SWS.
<>In conclusion, low doses of L-theanine can partially reverse caffeine-induced reductions in SWS; however, effects of L-theanine on caffeine-induced insomnia do not appear to increase dose-dependently."[238.06]

Vegetable Juicing

It is true when they say, "we should not juice fruits, but instead vegetables", not because people are aware of the toxicity fructose poses but because they inherently know consuming sugary drinks is not healthy, although there is danger of oxalate toxicity with vegetable juicing, if you do not juice vegetables high in oxalate you should be fine.

Red Cabbage

One of the healthiest vegetables to juice being a cruciferous vegetable, it enhances lifespan.

"<>Many studies have demonstrated that cabbages possess various biological activities, and our previous studies confirmed that cyanidin-3-diglucoside-5-glucoside (CY3D5G), the major core of red cabbage anthocyanins, exhibited in vitro antioxidant activity. This study further investigated the protective effects of CY3D5G derivative from red cabbage

juice (RCJ) on oxidative stress and lifespan in cells and Caenorhabditis elegans, green cabbage juice (GCJ) was used as control. RCJ rather than GCJ significantly improved cell viability and decreased lactate dehydrogenase release in H2O2-induced caco-2 cells. RCJ significantly increased survival during oxidative and heat stress and mean lifespan in C. elegans by 171.63% and 31.64%, and 28.16%, respectively, while GCJ treatment showed no significant effects ($p < 0.05$). These results might be attributed to significantly ($p < 0.05$) higher contents of total phenolics, ascorbic acid, glucosinolates, and anthocyanins in RCJ compared to those in GCJ.
<>Additionally, both of them decreased autofluorescence and reproductive capacity, increased body length, but did not alter the intracellular ROS level. Prolonged lifespan by RCJ might require heat-shock transcription factor pathway, sirtuin signaling, and calmodulin kinase II pathway, independent of insulin/insulin-like growth factor-1 signaling pathway. RCJ showed promising antioxidant properties in caco-2 cells and C. elegans, which provided more information on the health benefits of cabbage."[238.A]

Bell Pepper

These peppers (especially the yellow variety), being good sources of carotenoids, should be juiced every day in large quantities, if your budget permits it.

"<>The carotenoids of a yellow (F(1) Amanda hybrid) and a red (F(1) Magali hybrid) pepper (Capsicum annuum L.) at the ripe stage, marketed in Campinas, Brazil, were identified by the combined use of the chromatographic behavior, absorption spectra, and chemical reactions, confirmed by the mass spectra. HPLC was carried out with a Spherisorb ODS 2 (C18, monomeric, 3 microm, 4.6 x 150 mm) column and DAD and mass detector. The main carotenoids in the yellow pepper were violaxanthin (27.1-36.6 microg/g), lutein (5.3-9.3 microg/g), and beta-carotene (1.6-3.9 microg/g). Neoxanthin, (Z)-violaxanthin, (Z)-antheraxanthin, (Z)-lutein, alpha-cryptoxanthin, beta-cryptoxanthin, zeta-carotene, alpha-carotene, and phytofluene were also found as minor carotenoids. In red pepper, the major carotenoids were capsanthin (29.2-36.2 microg/g), lutein (5.8-8.7 microg/g), beta-carotene (5.1-6.8 microg/g), and violaxanthin (1.8-3.6 microg/g). Minor carotenoids were capsorubin, beta-apo-8'-carotenal, antheraxanthin, zeaxanthin, and beta-cryptoxanthin."[238.B]

Artichoke

The uneaten and discarded parts of Artichoke appear to contain a plethora of polyphenolic phytochemicals of interest.

"<>Artichoke waste represents a huge amount of discarded material. This study presents the by-products (bracts, exterior leaves, and stalks) of the "Blanca de Tudela" artichoke variety as a potential source of phenolic compounds with promising antioxidant

properties. Artichoke residues were subjected to different extraction processes, and the antioxidant capacity and phenolic composition of the extracts were analyzed by spectrophotometric methods and high performance liquid chromatography (HPLC) analyses, respectively.
<>The most abundant polyphenols in artichoke waste were chlorogenic acid, luteolin-7-O-rutinoside, and luteolin-7-O-glucoside. Minor quantities of cynarin, luteolin, apigenin-7-O-glucoside, apigenin-7-O-rutinoside, and naringenin-7-O-glucoside were also found. The antioxidant activity of the obtained extracts determined by ABTS [2, 2′-azinobis (3-ethylbenzothiazoline-6-sulphonic acid)], DPPH (2,2-diphenyl-1-pycrilhydracyl), and FRAP (Ferric Ion Reducing Antioxidant Power) was highly correlated with the total concentration of phenolic compounds. Chlorogenic acid, luteolin-7-O-glucoside, and luteolin-7-O-rutinoside, the most abundant compounds in 60% methanol extracts, are the components most responsible for the antioxidant activity of the artichoke waste extracts. The extract with the best antioxidant capacity was selected to assay its antioxidant potential on a model intestinal barrier. This action of the hydroxycinnamic acids on intestinal cells (Caco-2) was confirmed. In summary, artichoke waste may be considered a very interesting ingredient for food functionalization and for therapeutic purposes."[238.C]

Barley Grass

Barley Grass is a better antioxidant than Wheat Grass, but that does not mean you should not consume Wheat Grass Juice. It is suggested that you grow your own Barley Grass because the quality control regarding its commercial production and sale (Barley Grass Juice especially) is subpar, whereas Wheat Grass products have higher quality control standards.

[A] A comparison of the two grasses, showing Barley Grass to be superior.

"<>The present study was conducted to evaluate the phytochemical profile of green grasses including barley and wheat. Green grasses were procured from Ayub Agricultural Research Institute, Faisalabad, Pakistan. All the phytochemical parameters were determined through standard methods with slight modifications. The explored parameters include proximate analysis, mineral profile, vitamin profile, and especially antioxidant profile (total phenolic contents (TPCs), free radical scavenging activity, flavonoids, and phenolic acids).
<>The results portrayed that there was a significant difference between the proximate parameters, vitamin, and minerals profile of both barley and wheatgreen grasses. The antioxidant profile – antioxidant activity (283.5%) and free radical scavenging activity (99.29%) – of barley grass was much higher than wheatgrass. The TPCs (203.52 μmol of GAE/g) and flavonoids (161.12 μmol/L) were much higher in wheatgrass as compared to barley grass. Barley grass showed maximum contents of phenolic acids including benzoic

acid (73.84 μg/g), caffeic acid (86.61 μg/g), gallic acid (6.33 μg/g), syringic acid (170.46 μg/g), p-hydroxybenzoic acid (42.52 μg/g), and Ferulic acid (1560.3 μg/g). Conclusively, barley grass showed higher antioxidant potential."[238.D]

[B] Barley Grass for its high content of Ferulic Acid may promote hypertrophy of skeletal muscles through mTOR expression.

"<>As a widely distributed and natural existing antioxidant, ferulic acid and its functions have been extensively studied in recent decades. In the present study, hypertrophic growth of fast skeletal myofibers was observed in adult zebrafish after ferulic acid administration for 30 days, being reflected in increased body weight, body mass index (BMI), and muscle mass, along with an enlarged cross-sectional area of myofibers. qRT-PCR analyses demonstrated the up-regulation of relative mRNA expression levels of myogenic transcriptional factors (MyoD, myogenin and serum response factor (SRF)) and their target genes encoding sarcomeric unit proteins involved in muscular hypertrophy (skeletal alpha-actin, myosin heavy chain, tropomyosin, and troponin I). <>Western blot analyses detected a higher phosphorylated level of zTOR (zebrafish target of rapamycin), p70S6K, and 4E-BP1, which suggests an enhanced translation efficiency and protein synthesis capacity of fast skeletal muscle myofibers. These changes in transcription and translation finally converge and lead to higher protein contents in myofibers, as confirmed by elevated levels of myosin heavy chain (MyHC), and an increased muscle mass. To the best of our knowledge, these findings have been reported for the first time in vivo and suggest potential applications of ferulic acid as functional food additives and dietary supplements owing to its ability to promote muscle growth."[238.E]

[B2] Ferulic Acid promotes neurogenesis.

"<>Ferulic acid (4-hydroxy-3-methoxycinnamic acid; FA) is a plant constituent and is contained in several medicinal plants for clinical use. In this paper, we investigated the effects of FA on the proliferation of neural stem/progenitor cells (NSC/NPCs) in vitro and in vivo. FA significantly increased the proliferation of NSC/NPCs cultured from the telencephalon of embryonic day-14 rats, and increased the number and size of secondary formed neurospheres. An in vitro differentiation assay showed that FA did not affect the percentage of either neuron-specific class III beta-tubulin (Tuj-1)-positive cells or glial fibrillary acidic protein (GFAP)-positive cells in the total cell population. <>Oral administration of FA increased the number of newly generated cells in the dentate gyrus (DG) of the hippocampus of corticosterone (CORT)-treated mice, indicating that FA enhances the proliferation of adult NSC/NPCs in vivo. We also found that oral administration of FA increased cAMP response element binding protein (CREB) phosphorylation and brain-derived neurotrophic factor (BDNF) mRNA level in the hippocampus of CORT-treated mice, and ameliorated the stress-induced depression-like

behavior of mice. These novel pharmacological effects of FA may be useful for the treatment of mood disorders such as depression."[238.F]

Ginger Root

Ginger Root contains chemicals called Gingerols which are powerful antioxidants capable of suppressing the generation of most free radicals, but more interestingly, the consumption of fresh Ginger juice was shown to promote the growth of Firmicutes (Lactobacilli) and decrease the amount of Bacteroidetes (Phylum of Bacteroides) in human intestinal flora.

"<>Ginger, a widely used functional food and food additive, little is known about the effect of ginger juice, which is rich in many healthful agents, on healthy humans or on its relationship with gut microbiota composition variation. The aim of this study was to investigate the changes in the gut microbial communities that occur following the supplementation of fresh ginger-derived juice in healthy adults and its potential associations with function.
<>A crossover intervention study in which 123 healthy subjects (63 men and 60 women) consumed fresh ginger juice from Zingiber officinale Rosc. or sterile 0.9% sodium chloride was conducted. 16S rRNA sequencing analyses were applied to characterize gut microbiota variation.
<>We found that ginger juice intervention increased the species number of intestinal flora. A decreased relative abundance of the Prevotella-to-Bacteroides ratio and pro-inflammatory Ruminococcus_1 and Ruminococcus_2 while a tendency toward an increased Firmicutes-to-Bacteroidetes ratio, Proteobacteria and anti-inflammatory Faecalibacterium were found."[238.G]

Tomato

Tomatoes are excellent source of the carotenoid Lycopene, and other novel compounds that accelerate the metabolism and promote neurotrophic effects.

[A] High dosages of Lycopene promotes bDNF expression.

"<>Lycopene is a natural plant extract widely studied for its powerful antioxidant and neuroprotective effects. Emerging evidence suggests that it also possesses potential antidepressant properties. Compared to commonly used clinical antidepressants, lycopene offers higher safety; however, its underlying mechanisms remain unclear. Therefore, this study aims to explore the mechanisms through which lycopene exerts its antidepressant effects.

<>We employed the chronic social defeat stress (CSDS) model to induce depressive-like behaviors in mice, followed by lycopene treatment (20 mg/kg). Based on previous research, we focused on synaptic plasticity by examining the expression of synaptic proteins in the hippocampus to uncover potential mechanisms. The results showed that CSDS induced synaptic plasticity impairments in the hippocampus, but lycopene treatment significantly improved these synaptic deficits and reversed the depressive-like behaviors induced by CSDS.
<>Moreover, lycopene treatment upregulated the expression of brain-derived neurotrophic factor (BDNF) and reduced the activity of BDNF-TrkB/pTrkB pathway in the hippocampus. These molecular changes were consistent with changes in synaptic-related proteins, suggesting that lycopene may enhance synaptic plasticity via the BDNF-TrkB/pTrkB signaling pathway.
<>This study explored the mechanisms underlying depressive-like behaviors induced by CSDS in mice and provided preclinical evidence that lycopene may serve as a potential antidepressant. It offers an effective avenue for the development of novel antidepressant therapies."[238.H]

[B] Tomatoes contain the novel PPARa agonist 9-oxo-ODA. [See: Myokines]

"<>Dyslipidemia is a major risk factor for development of several obesity-related diseases. The peroxisome proliferator-activated receptor α (PPARα) is a ligand-activated transcription factor that regulates energy metabolism. Previously, we reported that 9-oxo-10,12-octadecadienoic acid (9-oxo-ODA) is presented in fresh tomato fruits and acts as a PPARα agonist. In addition to 9-oxo-ODA, we developed that 13-oxo-9,11-octadecadienoic acid (13-oxo-ODA), which is an isomer of 9-oxo-ODA, is present only in tomato juice.
<>In this study, we explored the possibility that 13-oxo-ODA acts as a PPARα agonist in vitro and whether its effect ameliorates dyslipidemia and hepatic steatosis in vivo. In vitro luciferase assay experiments revealed that 13-oxo-ODA significantly induced PPARα activation; moreover, the luciferase activity of 13-oxo-ODA was stronger than that of 9-oxo-ODA and conjugated linoleic acid (CLA), which is a precursor of 13-oxo-ODA and is well-known as a potent PPARα activator.
<>In addition to in vitro experiment, treatment with 13-oxo-ODA decreased the levels of plasma and hepatic triglycerides in obese KK-Ay mice fed a high-fat diet. In conclusion, our findings indicate that 13-oxo-ODA act as a potent PPARα agonist, suggesting a possibility to improve obesity-induced dyslipidemia and hepatic steatosis."[238.I]

Kale: For its high content of Vitamin-K1.

Immature Broccoli Florets: To form Sulforaphane.

Sauerkraut: As a liquid probiotic.

Purple Cauliflower: For its high content of Rutin and anthocyanins.

Anti-Inflammation (Antioxidant) Cycle Dietary Fats

Because Linoleic acid competes for entrance into our cells with Alpha-Linolenic acid, it is important to consume more Alpha-Linolenic than Linoleic acid in your diet, but never to neglect Linoleic acid. A 60-40% Ratio is suggested.

Docosahexaenoic Acid (DHA) / Eicosapentaenoic Acid (EPA)

[A] Commercial Fish oil products are likely to have higher concentrations of oxidized (decayed) DHA and EPA molecules. It is wise to use Omega-3 supplements (Carlson Labs suggested) that have undergone a "nitrogen flush" and / or contain Vitamin-E, to reduce the rate of oxidation.

"<>One of the main characteristics of Alzheimer's disease (AD) is the β-amyloid peptide (Aβ) generated by β- and γ-secretase processing of the amyloid precursor protein (APP). Previously it has been demonstrated that polyunsaturated fatty acids (PUFAs), especially docosahexaenoic acid (DHA), are associated with a reduced risk of AD caused by decreased Aβ production. However, in epidemiological studies and nutritional approaches, the outcomes of DHA-dependent treatment were partially controversial. <>PUFAs are very susceptible to reactive oxygen species and lipid peroxidation, which are increased during disease pathology. In line with published results, lipid peroxidation was elevated in human postmortem AD brains; especially 4-hydroxy-nonenal (HNE) was increased. To investigate whether lipid peroxidation is only a consequence or might also influence the processes leading to AD, we analyzed 7 different oxidized lipid species including 5 oxidized DHA derivatives and the lipid peroxidation products of ω-3 and ω-6 PUFAs, HNE and 4-hydroxy-hexenal, in human neuroblastoma cells and mouse mixed cortical neurons. In the presence of oxidized lipids Aβ and soluble β-secreted APP levels were elevated, whereas soluble α-secreted APP was decreased, suggesting a shift from the nonamyloidogenic to the amyloidogenic pathway of APP processing. Furthermore, β- and γ-secretase activity was increased by oxidized lipids via increased gene expression and additionally by a direct effect on β-secretase activity.
<>Importantly, only 1% oxidized DHA was sufficient to revert the protective effect of DHA and to significantly increase Aβ production. Therefore, our results emphasize the need to prevent DHA from oxidation in nutritional approaches and might help explain the divergent results of clinical DHA studies."[238.1]

[B] DHA promotes memory and potentiates exercise-induced neurogenesis.

"<>Omega-3 fatty acids (i.e. docosahexaenoic acid; DHA), similar to exercise, improve cognitive function, promote neuroplasticity, and protect against neurological lesion. In this study, we investigated a possible synergistic action between DHA dietary

supplementation and voluntary exercise on modulating synaptic plasticity and cognition. Rats received DHA dietary supplementation (1.25% DHA) with or without voluntary exercise for 12 days.
<>We found that the DHA-enriched diet significantly increased spatial learning ability, and these effects were enhanced by exercise. The DHA-enriched diet increased levels of pro-brain-derived neurotrophic factor (BDNF) and mature BDNF, whereas the additional application of exercise boosted the levels of both. Furthermore, the levels of the activated forms of CREB and synapsin I were incremented by the DHA-enriched diet with greater elevation by the concurrent application of exercise. While the DHA diet reduced hippocampal oxidized protein levels, a combination of a DHA diet and exercise resulted in a greater reduction rate. The levels of activated forms of hippocampal Akt and CaMKII were increased by the DHA-enriched diet, and with even greater elevation by a combination of diet and exercise. Akt and CaMKII signaling are crucial step by which BDNF exerts its action on synaptic plasticity and learning and memory. These results indicate that the DHA diet enhanced the effects of exercise on cognition and BDNF-related synaptic plasticity, a capacity that may be used to promote mental health and reduce risk of neurological disorders."[239]

[C] DHA prevents Palmitic acid-induced muscle atrophy.

"<>Background. Accumulation of free fatty acids leads to lipid-toxicity-associated skeletal muscle atrophy. Palmitate treatment reduces myoblast and myotube growth and causes apoptosis in vitro. It is not known if omega-3 fatty acids will protect muscle cells against palmitate toxicity. Therefore, we examined the effects of docosahexaenoic acid (DHA) on skeletal muscle growth.
<>Methods. Mouse myoblasts (C2C12) were differentiated to myotubes, and then treated with 0 or 0.5 mM palmitic acid or 0 or 0.1 mM DHA. Results. Intramyocellular lipid was increased in palmitate-treated cells but was prevented by DHA-palmitate cotreatment. Total AMPK increased in DHA+ palmitate-treated compared to palmitate only cells. RpS6 phosphorylation decreased after palmitate (-55%) and this was blunted by DHA+ palmitate (-35%) treatment. Palmitate treatment decreased PGC1α protein expression by 69%, but was increased 165% with DHA+ palmitate (P = 0.017) versus palmitate alone. While palmitate induced 25% and 90% atrophy in myotubes (after 48 hours and 96 hours, resp.), DHA+ palmitate treatment caused myotube hypertrophy of ~50% and 100% after 48 and 96 hours, respectively. <>Conclusion. These data show that DHA is protective against palmitate-induced atrophy. Although DHA did not activate the AMPK pathway, DHA treatment restored growth-signaling (i.e., rpS6) and rescued palmitate-induced muscle atrophy."[240]

[D] DHA/EPA suppress myogenesis, do not therefore consume them chronically while engaging in destructive physical training.

"<>This study was conducted to elucidate the biological effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on cell proliferation, differentiation and gene

expression in C2C12 myoblasts. C2C12 were treated with various concentrations of EPA or DHA under proliferation and differentiation conditions. Cell viability was analyzed using cell counting kit-8 assays (CCK-8). The Edu assays were performed to analyze cell proliferation. To analyze cell differentiation, the expressions of myogenic marker genes were determined at the transcriptional and translational levels by qRT-PCR, immunoblotting and immunofluorescence. Global gene expression patterns were characterized using RNA-sequencing. Phosphorylation levels of ERK and Akt were examined by immunoblotting.
<>Cell viability and proliferation was significantly inhibited after incubation with EPA (50 and 100 μM) or DHA (100 μM). Both EPA and DHA suppressed C2C12 myoblasts differentiation. RNA-sequencing analysis revealed that some muscle-related genes were significantly downregulated following EPA or DHA (50 μM) treatment, including insulin-like growth factor 2 (IGF-2), troponin T3 (Tnnt3), myoglobin (Mb), myosin light chain phosphorylatable fast skeletal muscle (Mylpf) and myosin heavy polypeptide 3 (Myh3). IGF-2 was crucial for the growth and differentiation of skeletal muscle and could activate the PI3K/Akt and the MAPK/ERK cascade. We found that EPA and DHA (50 μM) decreased the phosphorylation levels of ERK1/2 and Akt in C2C12 myoblasts. Thus, this study suggested that EPA and DHA exerted an inhibitory effect on myoblast proliferation and differentiation and downregulated muscle-related genes expression."[241]

[E] EPA is neurogenic through suppressing IL-1B and promoting bDNF.

"<>Purpose: Interleukin (IL)-1β can activate glial cells to trigger neuroinflammation and neurodegeneration. Lower omega (n)-3 polyunsaturated fatty acids (PUFAs) and lower n-3/n-6 PUFA ratios occur in the brain of patients with Alzheimer's disease (AD). We have previously reported that an n-3 PUFA, eicosapentaenoic acid (EPA), can improve memory and attenuate neurodegeneration-like changes in animal models of AD. However, whether and how EPA modulates glial cell activity and functions remains unclear.
<>The aim of this study was to test the hypothesis that EPA may attenuate neuroinflammation by inhibiting microglial activation and microglia-produced proinflammatory cytokines, and by enhancing the expression of astrocytes-produced neurotrophins and their receptors. Male Long-Evans rats were fed either palm oil supplemented diet or EPA supplemented diet for 42 days. On day 36 of diet feeding, rats received an intracerebroventricular injection of IL-1β or saline for 7 days. The glial activation, the expression of amyloid precursor protein (APP), calcium-dependent phospholipase (cPL) A2, brain-derived neurotrophic factor (BDNF) and its receptor, and PUFA profile in the hippocampus were analyzed. IL-1β elevated biomarkers of microglial CD11b and astrocyte GFAP expression, increased the expression of APP, tumor-necrosis factor (TNF)-α, but reduced BDNF and its receptor (TrKB). IL-1β also lowered n-3 EPA and docosapentaenoic acid concentrations but increased n-6 PUFAs and cPLA2 activity in the hippocampus. EPA supplement normalized the n-3 and n-6

PUFA profiles and cPLA2 levels, inhibited glial activation, reduced APP and TNF-α expression, as well as up-regulated BDNF and TrKB."[242]

[F] EPA delays mitochondrial aging.

"<>Mitochondrial dysfunction is often observed in aging skeletal muscle and is implicated in age-related declines in physical function. Early evidence suggests that dietary omega-3 polyunsaturated fatty acids (n-3 PUFAs) improve mitochondrial function. Here, we show that 10 weeks of dietary eicosapentaenoic acid (EPA) supplementation partially attenuated the age-related decline in mitochondrial function in mice, but this effect was not observed with docosahexaenoic acid (DHA). The improvement in mitochondrial function with EPA occurred in the absence of any changes in mitochondrial abundance or biogenesis, which was evaluated from RNA sequencing, large-scale proteomics, and direct measurements of muscle mitochondrial protein synthesis rates. We find that EPA improves muscle protein quality, specifically by decreasing mitochondrial protein carbamylation, a post-translational modification that is driven by inflammation.
<>These results demonstrate that EPA attenuated the age-related loss of mitochondrial function and improved mitochondrial protein quality through a mechanism that is likely linked with anti-inflammatory properties of n-3 PUFAs. Furthermore, we demonstrate that EPA and DHA exert some common biological effects (anticoagulation, anti-inflammatory, reduced FXR/RXR activation), but also exhibit many distinct biological effects, a finding that underscores the importance of evaluating the therapeutic potential of individual n-3 PUFAs."[243]

[G] EPA promotes slow twitch fiber growth through PPAR-delta and AMPK expression in myotubes.

“<>Muscle fiber type composition (% slow-twitch and % fast-twitch fibers) is associated with metabolism, with increased slow-twitch fibers alleviating metabolic disorders. Previously, we reported that dietary fish oil intake induced a muscle fiber-type transition in a slower direction in rats. The aim of this study was to determine the functionality of eicosapentaenoic acid (EPA), a unique fatty acid in fish oil, to skeletal muscle fiber type and metabolism in rats.
<>Here, we showed that dietary EPA promotes whole-body oxidative metabolism and improves muscle function by increasing proportion of slow-twitch type 1 fibers in rats. Transcriptomic and metabolomic analyses revealed that EPA supplementation activated the peroxisome proliferator-activated receptor δ (PPARδ) and AMP-activated protein kinase (AMPK) pathways in L6 myotube cultures, which potentially increasing slow-twitch fiber share.
<>This highlights the role of EPA as an exercise-mimetic dietary component that improves metabolism and muscle function, with potential benefits for health and athletic performance.”[243.1]

Alpha-Linolenic Acid

Alpha-Linolenic acid is a neglected fatty acid. It has numerous benefits for the brain and body. I suggest it be consumed by way of Chia Seed oil added to your protein shake, coffee, tea, or myogenic drink, or myogenic desserts.

[A] ALA promotes bDNF expression, especially in women.

"<>In this study, we examined the effect of the oral consumption of α-Linolenic acid (ALA) on blood levels of BDNF and Malondialdehyde (MDA) in healthy adult humans. 30 healthy volunteers, 15 men and 15 women, were selected randomly. Each individual served as his or her own control. Before consuming the Flaxseed oil capsules, 5cc blood from each individual was sampled in order to measure the plasma levels of BDNF and MDA as baseline controls. During the experiment, each individual was given 3 oral capsules of flaxseed oil, containing 500mg of alpha linolenic acid, daily for one week. Then, plasma levels of BDNF and MDA were tested.
<>The plasma levels of BDNF and MDA significantly ($P < 0.05$) increased in individuals who received the oral capsules of ALA. Plasma levels of BDNF increased more in the women in comparison with the men."[244]

[B] ALA is myogenic through enhancing FAK and hypertrophy.

"<>The flaxseed-enriched diet protected the dystrophic muscle from apoptosis and preserved muscle myogenesis by increasing the myogenin and alpha myosin heavy chain. Moreover, it restored the normal expression pattern of caveolin-3 thereby allowing protein retention at the sarcolemma. ALA reduced TNF-induced apoptosis in differentiating myoblasts and prevented the TNF-induced inhibition of myogenesis, as demonstrated by the increased expression of myogenin, myosin heavy chain and caveolin-3, while promoting myotube fusion. The in silico investigation revealed that FAK pathways may play a central role in the protective effects of ALA on myogenesis."[245]

[C] ALA prevents muscle atrophy.

"<>Impaired regeneration and consequent muscle wasting is a major feature of muscle degenerative diseases. Nutritional interventions such as adjuvant strategy for preventing these conditions are recently gaining increasing attention. Ingestion of n3-polyunsaturated fatty acids has been suggested as having a positive impact on muscle diseases. We recently demonstrated that a diet enriched with plant derived n3-fatty acid, α-linolenic acid (ALA), exerts potent beneficial effects in preserving skeletal muscle regeneration in models of muscle dystrophy. To better elucidate the underlying mechanism we here investigate on the expression level of the anti- and pro-apoptotic proteins, as well as caspase-3 activity, in C2C12 myoblasts challenged with pathological levels of tumor necrosis factor-α (TNF).

<>The results demonstrated that ALA protective effect on C2C12 myoblasts was associated with a decrease in caspase-3 activity and an increase of the Bcl-2/Bax ratio. Indeed, the effect of ALA was directed to rescuing Bcl-2 expression and to revert Bax translocation to mitochondria both affected in an opposite way by TNF, a major pro-inflammatory cytokine expressed in damaged skeletal muscle. Therefore, ALA counteracts inflammatory signals in the muscle microenvironment and may represent a valuable strategy for ameliorating skeletal muscle pathologies."[246]

MCT oil: Caprylic (Octanoic Acid) / Capric Acid

Medium Chain Triglycerides such as Caprylic Acid and Capric Acid, although sharing similarities to the effects of Lauric Acid, have been shown in certain studies to reduce angiogenesis, therefore they have been placed within the Anti-Cycle.

[A] Caprylic Acid is neurogenic through promoting NGF.

"<>It has been shown that polyunsaturated fatty acids such as arachinonic and docosahexanoic acids but not monounsaturated and saturated long-chain fatty acids promote basal and nerve growth factor (NGF)-induced neurite extension of PC12 cells, a line derived from a rat pheochromocytoma. On the other hand, short-chain fatty acids and valproic acid (2-propylpentanoic acid) enhance the growth of neurite processes of the cells only in the presence of inducers. In this study, we demonstrated that straight medium-chain fatty acids (MCFAs) at millimolar concentrations alone potently induced neuronal differentiation of PC12 cells. Hexanoic, heptanoic and octanoic acids dose-dependently induced neurite outgrowth of the cells: their maximal effects determined 2 days after addition to the culture medium were more marked than the effect of NGF. <>PC12 cells exposed to octanoic acid expressed increased levels of the neuronal marker beta-tubulin isotype III. Nonanoic, decanoic, and dodecanoic acids also induced growth of neurite processes, but their maximal effects were less marked than that of octanoic acid. In contrast, the polyunsaturated fatty acid linoleic acid and short-chain fatty acids had only slight or almost no effects on neurite formation in the absence of NGF. The effect of octanoic acid was synergistic with or additive to the effects of NGF and dibutyryl cyclic AMP. Octanoic acid upregulated phosphorylation of p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK), and c-Jun N-terminal kinase (JNK), critical signaling molecules in neuronal differentiation, but not phosphorylation of Akt, a signaling molecule downstream of phosphatidylinositol 3-kinase (PI3K).
<>Moreover, growth of neurites induced by octanoic acid was potently inhibited by treatment of cells with the p38 MAPK inhibitor SB203580 and the ERK kinase inhibitor PD98059 but not inhibited and only slightly inhibited by the JNK inhibitor SP600125 and the PI3K inhibitor wortmannin, respectively. Taken together, our results indicate that MCFAs, including octanoic acid, induced neurite outgrowth of PC12 cells in the absence of NGF and suggest that the activation of p38 MAPK and ERK pathways is involved in this process."[247]

[B] Capric Acid is lipolytic and anabolic through promoting UCP3.

"<>Uncoupling protein 3 (UCP3) and pyruvate dehydrogenase kinase 4 (PDK4) in skeletal muscle are key regulators of the glucose and lipid metabolic processes that are involved in insulin resistance. Medium-chain fatty acids (MCFAs) have anti-obesogenic effects in rodents and humans, while long-chain fatty acids (LCFAs) cause increases in body weight and insulin resistance. To clarify the beneficial effects of MCFAs, we examined UCP3 and PDK4 expression in skeletal muscles of mice fed a MCFA- or LCFA-enriched high-fat diet (HFD). Five-week feeding of the LCFA-enriched HFD caused high body weight gain and induced glucose intolerance in mice, compared with those in mice fed the MCFA-enriched HFD. However, the amounts of UCP3 and PDK4 transcripts in the skeletal muscle of mice fed the MCFA- or LCFA-enriched HFD were similar.
<>To further elucidate the specific effects of MCFAs, such as capric acid (C10:0), on lipid metabolism in skeletal muscles, we examined the effects of various FAs on expression of UCP3 and PDK4, in mouse C2C12 myocytes. Although palmitic acid (C16:0) and lauric acid (C12:0) significantly induced expression of both UCP3 and PDK4, capric acid (C10:0) upregulated only UCP3 expression via activation of peroxisome proliferator-activated receptor-δ.
<>Furthermore, palmitic acid (C16:0) disturbed the insulin-induced phosphorylation of Akt, while MCFAs, including lauric (C12:0), capric (C10:0), and caprylic acid (C12:0), did not. These results suggest that capric acid (C10:0) increases the capacity for fatty acid oxidation without inhibiting glycolysis in skeletal muscle."[248]

[C] UCP3 positively participates in myogenesis.

"C2C12 myoblasts were cotransfected with expression vectors for myogenin and/or MyoD as well as reporter constructs. The simultaneous expression of myogenin and MyoD caused an additional 20-fold increase in the reporter expression via the UCP3 promoter, but only a weak effect via the UCP2 promoter. In L6 myoblasts, only MyoD activated the UCP3 promoter, but in 3T3-L1 cells neither factor activated the UCP3 promoter, indicating that additional cofactors are required, which are present only in C2C12 myoblasts. The expression of UCP2 and UCP3 is differentially regulated during muscle differentiation due to the different responsiveness of their promoter regions to myogenin and MyoD."[249]

Anti-Inflammation (Antioxidant) Cycle Diet

On this diet one should consume 2-4 Cups of Cruciferous Vegetables with each meal, predominately frozen broccoli florets or frozen cauliflower florets that have been microwaved in a microwave safe glass container, size 8-11 cups, with a lid on but cracked open at one corner, effectively steam cooking them during cooking (to avoid breaking down the antioxidants to a significant degree), with Grapeseed oil, Hempseed

oil, or a Polyphenol-rich EVOO Hybrid oil drizzled on top of each meal after cooking, and Edible Flowers sprinkled on top. Every meal should contain one fermented food, sauerkraut or low sugar kimchi are the ideal choices. You should also consider eating more purine-rich foods, to increase your blood uric acid content. [See: Bonus Information: Hyperuricemia Intelligentsia]

Chia Seed oil is best paired, for flavors' sake, with protein shakes or sweetened food, such as those made with grains. Consider adding it to your Myogenic Drink, Myogenic Dessert, or homemade breads.

If you wish to add a large amount of sweet and grainy slow digesting carbohydrates to each meal, make my *ALA Beta-Glucan Bread* (low risibility due to the rye, more of a brownie): 40% Dark Rye Flour + 30% Oat Flour Bread + 30% Golden Flaxmeal + Chia Seed oil + Instant Yeast + GlySer + Apple Cider Vinegar: Bake at 370 Degrees until golden brown. Cut into portioned pieces to be served with each meal. The second and easier option is to add half a can, or a full can of Organic Dark Red Kidney Beans, which possess a very low Glycemic Index.

As for protein consumption, Chicken, Wild Caught Fish, Turkey, & 95+% Lean Beef are permitted, stay away from pork, & soy products. It is not a bad idea to cycle between a carnivorous diet on your Pro-Cycle and a vegetarian diet on your Anti-Cycle, morality aside, because they each have benefits for the body and mind. If you replace your animal protein for primarily beans, although you will be restricting your total daily protein intake, if you continue, and you absolutely should, consuming a large amount (60g) of protein powder split between pre / post-workout, such as Pea Protein or Pumpkin seed protein powder, and GlySer throughout the day, you will be able to at the very least maintain any muscle mass you have accrued. This is the only form of Protein Restriction for lifespan extension I consider safe and effective over long durations because it still includes spikes of hyperaminoacidemia.

There are many Myogenic Deserts to be made, such as a homemade Oat Paste Chia Seed Pudding with GlySer, or Banana Coconut Milk Pudding with GlySer, or Rye-Oat & Flaxmeal Brownies, the possibilities are endless.

As for actual sugar, if you are taking expensive Probiotic Supplements, there is no reason not to consume sugar with them, in the form of at least one meal or snack per day, to enhance their *digestive survivability*.

Because Alpha-Linolenic acid and Linoleic acid compete with each other, like amino acids, for entry into our cells, you should ensure that for every gram of LA you consume, two grams or more of ALA are consumed each day to thereby experience the maximal cellular distribution and antioxidant affects ALA has to offer.

Edible Flowers

Edible Flowers are the future of medicine—that is to say, color is the future of medicine, for the phytochemicals (carotenoids / flavonoids) that give plants their most vibrant colors are the most beautiful antioxidants in existence. You should add these antioxidant rich flower petals to each meal, make tea from them, or if you've collected enough, you

can add them to your health smoothies. Although in the future we will only be microdosing flower petal phytochemicals, due to their expected sustained high cost, I believe that these phytochemicals are far more potent than one would expect. Because there is a limited demand currently for edible flowers (2025), aside from a select few, such as Hibiscus Sabdariffa, the flowers below will have to be grown, or purchased from a nursery, with the latter option being expensive. But this lack of industry is not a bad thing, as it is a good excuse to begin growing plants, and pursue a hobby in horticulture and botany, inside or outside of your house, to enrich your life through undertaking a relaxing intellectual pursuit.

I sincerely hope that after this book is published, the demand for edible flowers increases progressively, so that their phytochemical majesty is harnessed by those creative enough to utilize their beauty for their true purposes—for the promotion of health and wellness, rather than simple visual appeal. There is no doubt that one day we will deliver edible flowers bouquets to our loved ones, and those who are sickly, to be consumed not only by the eyes.

Daylily Flowers (Hemerocallis)

"<>The Hemerocallis accessions is widely consumed as nutritious vegetable and traditional medicine in eastern Asia and used as an ornamental flower worldwide. Compared with most other horticultural products, its flower is richer in polyphenols, flavonoids, carotenoids, and anthocyanins. Therefore, the flower has strong antioxidant activity that inhibits cancer cell proliferation, which could be used for health and pharmaceutical purposes. The flavonoids composition and distribution in the flowers, and the content varied between different accessions is still unclear.
<>In this context, eight flavonols, two flavones, and two anthocyanins were determined in Hemerocallis flower by high-performance liquid chromatography (HPLC) coupled with photodiode array and mass spectrometric detectors. Rutin was the most abundant flavonols and cyanidin 3,5-glucoside and cyanidin 3-rutinoside were the major anthocyanins in Hemerocallis tepals, resulting in flower petal coloration, and their content in the petal was higher than that of the sepal.[251.A]

Marigold Flowers (Tagetes Erecta)

"<>Commercially prepared marigold flower (Tagetes erecta) extract was saponified and analyzed for carotenoid composition. HPLC analyses were performed on two normal-phase columns (β-Cyclobond and silica) and on a C_{30} reversed-phase column. The extract contained 93% utilizable pigments (detected at 450 nm), consisting of all-trans and cis isomers of zeaxanthin (5%), all-trans and cis isomers of lutein, and lutein esters (88%). All were identified by chromatographic retention, UV−visible spectra, and positive ion electrospray mass spectrometry in comparison to authentic standards. Contrary to previous findings, insignificant levels (<0.3%) of lutein oxidation products were detected in the saponified extract. This compositional determination is important for the application of marigold extract in nutritional supplements and increases its value as a poultry feed colorant because it contains more biologically useful lutein compounds than previously believed."[251.B]

Pansy Flowers (Viola x Wittrockiana)

"<>The use of edible flowers has become increasingly popular as a good source of bioactive compounds. Many flowers can be consumed, but there is a lack of information about the chemical composition of organic and conventional flowers. Organic crops represent a higher level of food safety because pesticides and artificial fertilizers are prohibited. The present experiment was carried out with organic and conventional edible pansy flowers of different colors: double-pigmented violet/yellow and single-pigmented yellow flowers. In fresh flowers, the contents of dry matter and polyphenols (including phenolic acids, flavonoids, anthocyanins, carotenoids, and chlorophylls) and the antioxidant activity were determined by the HPLC-DAD method.
<>The results showed that organic edible pansy flowers contained significantly more bioactive compounds, especially polyphenols (333.8 mg/100 g F.W.), phenolic acids

(40.1 mg/100 g F.W.), and anthocyanins (293.7 mg/100 g F.W.) compared to conventional methods. Double-pigmented (violet/yellow) pansy flowers are more recommended for the daily diet than single-pigmented yellow flowers. The results are unique and open the first chapter in a book on the nutritional value of organic and conventional edible flowers."[251.C]

Hardy Fuchsia Flowers (Fuchsia Magellanica)

"<>Unusual quercetin galloyl hexosides (46, 50, 53) and a kaempferol galloyl hexoside (58) were detected in Fuchsia samples and primarily in F. magellanica. Even if anthocyanins were predominant, a peonidin dihexoside isomer (V) was present in each Fuchsia sample, while cyanidin dihexoside (II) was described only in F. magellanica extracts.
<>Anthocyanins are strong antioxidant compounds and their scavenging activity corresponds with their structural characteristics as well, di-acylated forms possess higher antioxidant activity than the mono-acylated and non-acylated anthocyanins. Sun et al. demonstrated that peonidin and cyanidin-based anthocyanins exert strong antioxidant properties."[251.D]

Orange Impatiens Flowers (Impatiens Wallerana)

One should grow or purchase the Orange versus Pink variety owing to the more potent antioxidant effect of Pelargonidin over Malvidin.

"<>A factor that was also observed in this study was that the anthocyanin composition of the rose petals was different from the composition of the orange petals, which is in accordance with the major anthocyanin compounds found in both samples. Meaning, the orange samples presented highest concentrations in pelargonidin derivatives, followed by peonidin derivatives, explaining its orange colour. On the other hand, the pink samples presented the highest amounts of malvidin derivatives followed by pelargonidin derivatives, explaining their pink colour."[251.E]

Lilac Flowers (Syringa Vulgaris)

"<>Significant amounts of free or glycosylated chemical components belonging to various therapeutically important structural classes, such as phenyl-propanoids (syringin, acteoside, echinacoside), flavonoids (quercetin, kaempferol derivatives) and secoiridoids (secologanoside, oleuropein, 10-hydroxy oleuropein, demethyloleuropein, syringalactone A, nuzhenide, lingstroside) were obtained for the flowers, leaves and bark extracts, respectively. Furthermore, MTT tests pointed out a significant cytotoxic potential expressed in a non-dose-dependent manner toward the tumoral lines. The performed methods underlined that S. vulgaris extracts, in particular belonging to flowers and leaves, represent valuable sources of compounds with antioxidant and antitumoral potential.

<>Our study revealed that the flowers extract showed significant ($p < 0.001$) higher antioxidant activity ($IC50 = 36.83$ µg/mL) compared to the other analyzed extracts in the following order: flowers > leaves > bark > fruit (Table 9). The similar results for flowers extract were obtained by CUPRAC and FRAP assays ($p < 0.001$). Moreover, the present study brings originality by offering, for the first time, proof of antioxidant capacity of the tested samples by different other mechanisms that are highlighted using the two other assays, FRAP and CUPRAC. At the same time, the study offers for the first time a comparative view on flowers, fruit, leaves and bark, bringing evidence on the fact that flowers represent the most important antioxidant potential."[251.F]

Yellow Primula x Polyantha Flowers

For its high content of Laricitrin & Syringetin, both of which are flavonols that enhance lifespan.

[A] "<>Yellow primrose was characterized by the greatest diversity of flavonols as it contained four isorhamnetin, five kaempferol, six laricitrin, three myricetin, six quercetin, and six syringetin glycosides."

[B] A study on the life extending effects of Laricitrin and Syringetin.

"<>Only certain flavonoids have been shown to enhance life span. This was pointed out for e.g. myricetin in the nematode Caenorhabditis elegans. However, the structural requirements responsible for this effect are not known. We used methylated derivatives of myricetin (laricitrin, syringetin, myricetintrimethylether) to investigate if free OH moieties in the B-ring are necessary for the life span extending effect. In analogy to myricetin, all derivatives increased the life span, decreased oxidative stress (DCF) and decreased the accumulation of lipofuscin. In contrast to myricetin, the methylated compounds strongly enhanced the resistance against thermal stress. Furthermore, treatment with the derivatives induced a much stronger nuclear localization of the DAF-16 transcription factor (FoxO homologue).
<>Additionally, no antioxidant effects and only minor effects on life span prolongation and stress resistance were detectable for the methylated compounds in a DAF-16 deficient nematode strain. Comparable to the dietary flavonoid myricetin, the methylated myricetin derivatives laricitrin, syringetin and myricetintrimethylether strongly enhance the life span of C. elegans. Therefore, OH groups of ring B are not necessary for this effect. Only the methylated compounds increase the stress resistance of the nematode which was dependent on DAF-16. These findings suggest that methylation of myricetin increases the biofunctionality."[251.G]

Anti-Inflammation (Antioxidant) Cycle Modalities

Hyperthermia Therapy (Sauna).

Hyperthermia is a modality for both cycles, as it accelerates wound healing. An excellent idea is to add Eucalyptus Globulus oil to an at home steam sauna to facilitate total body saturation in 1,8-Cineole and delay superficial aging. It must be mentioned that Hyperthermia is inflammatory, it results in the generation of ROS and may damage the brain, you should therefore save your highest heat sauna sessions for the Anti-Cycle and engage in lower heat, longer duration sauna sessions on a Pro-Cycle. Considering that sweating results in the rapid excretion of electrolytes, B-Vitamins, and zinc, it is not intelligent to abuse Hyperthermia Therapy on a Pro-Cycle as you will assuredly develop severe nutrient deficiencies which will first be noticed through the development of muscle cramps. Furthermore, the older you are the less heat tolerance you will have, meaning you should progressively move towards more frequent Ice Bath sessions, or Ice Walks (minimal clothing) and less frequent Sauna sessions as you age, depending on how intense you trained in the day, and how many antioxidants you are using, such that if you are on a myriad of essential nutrients and phytochemicals, you should in hypothesis continue to experience benefits from Hyperthermia Therapy, even if they are blunted, while mitigating or prevent the inflammatory side effects.
Although there exists contradictory research on heat and angiogenesis, it is true that the inflammatory (pro-ROS) nature of intense Hyperthermia Therapy may perturb angiogenesis through mitochondrial destabilization, this will not be an issue if your goal is to promote IL-6 expression post-exercise, but if brain or muscle angiogenesis is your goal, it may be wise to ensure that your Hyperthermia Therapy is of moderate intensity such that your heart rate does not climb steadily, and you do not become light headed during therapy, as these are signs of intense physiological heat stress.

On the following page is a clear and simple guideline for Hyperthermia Therapy to protect brain cells against excessive, or high frequency hyperthermic damage.

IMC Hyperthermia Therapy Guidelines

Intense Hyperthermia (Sauna / Steam):
Anti-Cycle = Unlimited
Pro-Cycle = 1-2 Days / Week

Moderate Hyperthermia (Bath, Jacuzzi):
Anti-Cycle = Unlimited
Pro-Cycle = Unlimited

If you prefer hot bathes, they can in fact be good forms of Hyperthermia Therapy, if you fill the bath water with conditioner and Epsom salt to mitigate the absorption of heavy metals and other tap water toxins. A good protocol for hot bath hyperthermia is to fill a bathtub with moderately hot water, get in, and then begin running a small stream of super-hot water, so that there's a constant influx of hot water, and then you lean back and submerge as much of your body as possible, and while submerged slowly rock your body in a prone position back and forth, creating a gentle current that will spread the incoming heat throughout the bath, while periodically sitting up and leaning forward, submerging your arms into the water, as a ten or twenty second respite from the discomfort of increasing heat, doing this for around twenty-thirty minutes, until your heart rate piques and you feel uncomfortable. If you followed this idea correctly, after exiting the bath you should sweat profusely as the body deals with the residual hyperthermic stress. This Progressive Bath Hyperthermia Therapy is to be considered bordering on Intense Hyperthermia Therapy.

[A] Hyperthermia is myogenic 1: through activating the androgen receptors.

"<>To elucidate the functional significance of heat-shock protein beta 1 (HSPB1) in androgen-mediated myogenesis of bovine cells, we conducted 'loss and gain of function of HSPB1' assays by siRNA inhibition and gene overexpression. siRNA inhibition of HSPB1 expression reduced the expression of desmin (a myogenic marker) and repressed the formation of myotubes in cells induced for myogenic differentiation.
<>In contrast, overexpression of HSPB1 enhanced the expression of desmin and accelerated formation of myotubes. The loss and gain of HSPB1 function was closely associated with the expression level of androgen receptor (AR).
<>Our findings suggest that HSPB1 mediates androgen signaling by binding directly to AR and then enhancing androgen-mediated myogenesis in myogenic cells."[252]

[B] Hyperthermia is myogenic 2: Through reducing muscle damage.

"<>Skeletal muscle reloading following disuse is characterized by profound oxidative damage. This study tested the hypothesis that intermittent hyperthermia during reloading attenuates oxidative damage and augments skeletal muscle regrowth following immobilization. Forty animals were randomly divided into four groups: control (Con), immobilized (Im), reloaded (RC), and reloaded and heated (RH). All groups but Con were immobilized for 7 days. Animals in the RC and RH groups were then reloaded for 7 days with (RH) or without (RC) hyperthermia (41-41.5 degrees C for 30 min on alternating days) during reloading. Heating resulted in approximately 25% elevation in heat shock protein expression ($P < 0.05$) and an approximately 30% greater soleus regrowth ($P < 0.05$) in RH compared with RC.
<>Furthermore, oxidant damage was lower in the RH group compared with RC because nitrotyrosine and 4-hydroxy-2-nonenol were returned to near baseline when heating was combined with reloading. Reduced oxidant damage was independent of antioxidant

enzymes (manganese superoxide dismutase, copper-zinc superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase).
<>In summary, these data suggest that intermittent hyperthermia during reloading attenuates oxidative stress and improves the rate of skeletal muscle regrowth during reloading after immobilization."[253]

[C] Hyperthermia enhances angiogenesis & reduces muscle atrophy proteins.

"<>The purpose of this study was to investigate the influence of heat treatment on glucocorticoid (GC)-induced myopathy. Eight-week-old Wistar rats were randomly assigned to the control, Dex, and Dex + Heat groups. Dexamethasone (2 mg/kg) was injected subcutaneously 6 days per week for 2 weeks in the Dex and Dex + Heat group. In the Dex + Heat group, heat treatment was performed by immersing hindlimbs in water at 42 °C for 60 min, once every 3 days for 2 weeks. The extensor digitorum longus muscle was extracted following 2 weeks of experimentation.
<>In the Dex + Heat group, muscle fiber diameter, capillary/muscle fiber ratio, and level of heat shock protein 72 were significantly higher and atrogene expression levels were significantly lower than in the Dex group. Our results suggest that heat treatment inhibits the development of GC-induced myopathy by decreasing atrogene expression and increasing angiogenesis. "[254]

[D] Hyperthermia may damage the testis through ROS generation which damages mitochondria, which leads to excessive autophagy, that of which damages cells beyond repair.

“<>As a key factor in determining testis size and sperm number, sertoli cells (SCs) play a crucial role in male infertility. Heat stress (HS) reduces SCs counts, negatively impacting nutrient transport and supply to germ cells, and leading to spermatogenesis failure in humans and animals. However, how HS affects the number of SCs remains unclear. We hypothesized that changes in SC metabolism contribute to the adverse effects of HS. In this study, we first observed an upregulation of arachidonic acid (AA), an unsaturated fatty acid after HS exposure by LC-MS/MS metabolome detection. By increasing ROS levels, expression of KEAP1 and NRF2 proteins as well as LC3 and LAMP2, 100 μM AA induced autophagy in SCs by activating oxidative stress (OS).
<>We observed adverse effects of AA on mitochondria under HS with a decrease of mitochondrial number and an increase of mitochondrial membrane potential (MMP). We also found that AA alternated the oxygen transport and absorption function of mitochondria by increasing glycolysis flux and decreasing oxygen consumption rate as well as the expression of mitochondrial electron transport chain (ETC) proteins Complex I, II, V. However, pretreatment with 5 mM NAC (ROS inhibitor) and 2 μM Rotenone (mitochondrial ETC inhibitor) reversed the autophagy induced by AA.
<>In summary, AA modulates autophagy in SCs during HS by disrupting mitochondrial ETC function, inferring that the release of AA is a switch-like response, and providing

insight into the underlying mechanism of high temperatures causing male infertility."[254.1]

[E] Hyperthermia appears to stimulate autophagy, but older individuals appear to experience greater inflammatory effects following Hyperthermia exposure, meaning that they should reserve its use for the Anti-Cycle only where antioxidants can be used to quell excessive inflammation, yet there is no doubt Heat Shock Proteins will still exert anabolic effects into old age.

"<>With rising global temperatures, heat-related mortality is increasing, particularly among older adults. Although this is often attributed to declines in thermoregulatory function, little is known regarding the effect of age on the cellular processes associated with mitigating heat-induced cytotoxicity. We compared key components of the cellular stress response in 19 young (19-31 yr; 10 female) and 37 older adults (61-78 yr; 10 female) during 9 h of heat exposure (40°C, 9% relative humidity). Mean body temperature (Tbody) was calculated from core and skin temperatures. Changes in proteins associated with autophagy, apoptotic signaling, acute inflammation, and the heat shock response were assessed via Western blot in peripheral blood mononuclear cells harvested before and after exposure. Tbody increased by 1.5 (SD 0.3)°C and 1.7 (0.3)°C in the young and older adults, respectively. We observed similar elevations in autophagy-related proteins (LC3-II and LC3-II/I) in young and older adults (both $P \geq 0.121$). <>However, the older adults displayed signs of autophagic dysfunction, evidenced by a 3.7-fold [95% CI: 2.4, 5.6] greater elevation in the selective autophagy receptor p62 ($P < 0.001$). This was paired with elevations in apoptotic responses, with a 1.7-fold [1.3, 2.3] increase in cleaved caspase-3 in the older relative to young adults ($P < 0.001$). Older adults also exhibited diminished heat shock protein 90 responses (0.7-fold [0.5, 0.9] vs. young, $P = 0.011$) and, at any given level of thermal strain (Tbody area under the curve), elevated tumor necrosis factor-α (1.5-fold [1.0, 2.5] vs. young, $P = 0.008$). Attenuated autophagic responses may underlie greater vulnerability to heat-induced cellular injury in older adults.
<>NEW & NOTEWORTHY We demonstrate for the first time that peripheral blood mononuclear cells from older adults exhibit signs of autophagic impairments during daylong (9 h) heat exposure relative to their younger counterparts. This was paired with greater apoptotic signaling and inflammatory responses, and an inability to stimulate components of the heat shock response. Thus, autophagic dysregulation during prolonged heat exposure may contribute to age-related heat vulnerability during hot weather and heat waves."[254.2]

Topical Heat Therapy (Heat Pad Therapy)

Topical Heat Therapy is another modality for each cycle and a great way to promote the targeted wound healing of muscles, depending on the duration of use and the level of heat of the device you use. I believe if you are able to locate a heat pad that is large enough,

and one that produces an adequately high level of heat, you will be able to promote noticeably faster recovery of primarily limb muscles.

The age old remedy for a muscle injury has been to apply ice to the injured area, but this is unfortunately directly counterintuitive to promoting the process of wound healing, and may very well be detrimental, as the earliest stage of wound healing requires blood flow, angiogenesis, and other inflammatory processes.

A good application time of heat pad therapy is an hour or more per day, primarily post-workout, with everyday use being most effective.

Hypothermia Therapy (Cryotherapy: Ice Baths)

This modality will only enhance fat loss to a noticeable *degree* if done multiple times a day[1], or for an extended period of time (at a greater risk), rendering commercial cryotherapy useless and overpriced. Aside from the lipolytic benefits of hypothermia therapy, it can be safely assumed that whereas mild hyperthermia accelerates cellular processes, mild hypothermia will decelerate them, thereby extending lifespan through a reduction in cellular respiration, or through a reduction in DNA strand breaks.

I am under the opinion that extended duration mild Hypothermia Therapy (60-120 Minutes per day) is more beneficial to the human body than intermittent chronic Hypothermia Therapy.

It is much more intelligent to invest in a small or large restaurant ice maker and take Ice Baths at home, rather than pay the premium price for advanced forms of cryotherapy, selfsame to investing in a dry heat sauna at home (or small form steam sauna). Allowing corporations to control your access to thermal therapies is not only expensive but dangerous and inconvenient, you should always attempt to be in complete control of your health by turning your home into a biomedical clinic.

Interestingly, hypothermia reduces cellular respiration but promotes lipolysis, and this may seem contradictory, but it is not, as during hypothermia therapy thermogenesis increases in brown fat, leading to increased energy expenditure i.e. increased metabolism in specialized regions of the body, this occurs through UCP1 expression[2]. Brown fat thermogenesis is not the sole reason for hypothermic lipolysis as white fat lipolysis also occurs rapidly following hypothermia in fasted states resulting from norepinephrine release (sympathetic nervous system activation) and the resultant increase in Hormone-sensitive Lipase[3].

As for this therapy's timing, in theory, evening Cold Exposure makes the most sense, but it does not make sense to take an Ice Bath after a strenuous workout, therefore when you choose to engage in Hypothermia Therapy should depend soley on when you perform your most strenuous workouts, such that if you enjoy strength training or engaging in intense cardio in the morning, you can save the Ice Bath for the evening, but if you enjoy training heavy and hard in the evening, before bed, it does not make sense to constrict blood vessels post-workout with cold exposure, even on an Anti-Cycle, therefore you should take your Ice Bath in the morning, and Sauna in the evening, although it must be mentioned that if you do not rapidly cool your body post-

Hyperthermia Therapy in hours leading up to sleep, with an iced drink, such as a Wild Blueberry Smoothie, you may perturb your sleep.

[1] "<>Background: Local adipose tissue (AT) cooling is used to manage obesity and overweight, but the mechanism is unclear. The current view is that acute local cooling of AT induces adipocyte cell disruption and inflammation ("cryolipolysis") that lead to adipocyte cell death, with loss of subcutaneous fat being recorded over a prolonged period of weeks/months. A contrasting view is that AT loss via targeted cryotherapy might be mediated by thermogenic fat metabolism without cell disruption.
<>Methods: In this retrospective study of individuals presenting for cryotherapy to the Clinic BioEsthetic, Paris, France, we recorded waist circumference, body weight, and body mass index (BMI) by direct measurement and by whole-body dual-energy X-ray absorptiometric scanning. In select individuals, blood analysis of markers of inflammation and fat mobilization was performed before and after the procedure.
<>Results: We report that (i) single sessions of tissue cryotherapy lead to significant loss of tissue volume in the time frame of hours and (ii) multiple daily procedures lead to a cumulative decline in AT, as assessed by waist circumference, body weight, and BMI, confirmed by whole-body dual-energy X-ray absorptiometric scanning. In addition, (iii) blood analysis following tissue cryotherapy found no significant changes in biochemical parameters including markers of inflammation. Moreover, (iv) calculations of heat extracted and of compensatory weight loss taking place through thermogenesis are substantially consistent with the observed loss of AT.
<>Conclusions: These findings argue that cold-induced thermogenesis ("cryothermogenesis") rather than adipocyte disruption underlies the reduction in AT volume, raising the prospect that more intensive cryotherapy may be a viable option for combating obesity and overweight."[255]

[2] "<>That uncoupling protein 1 (UCP1) is the sole mediator of adipocyte thermogenesis is a conventional viewpoint that has primarily been inferred from the attenuation of the thermogenic output of mice genetically lacking Ucp1 from birth (germline Ucp1-/-). However, germline Ucp1-/- mice harbor secondary changes within brown adipose tissue. To mitigate these potentially confounding ancillary changes, we constructed mice with inducible adipocyte-selective Ucp1 disruption. <>We find that, although germline Ucp1-/- mice succumb to cold-induced hypothermia with complete penetrance, most mice with the inducible deletion of Ucp1 maintain homeothermy in the cold. However, inducible adipocyte-selective co-deletion of Ucp1 and creatine kinase b (Ckb, an effector of UCP1-independent thermogenesis) exacerbates cold intolerance. Following UCP1 deletion or UCP1/CKB co-deletion from mature adipocytes, moderate cold exposure triggers the regeneration of mature brown adipocytes that coordinately restore UCP1 and CKB expression. Our findings suggest that thermogenic adipocytes utilize non-paralogous protein redundancy-through UCP1 and CKB-to promote cold-induced energy dissipation."[255.1]

[3] "<>Lipid droplet (LD) lipolysis in brown adipose tissue (BAT) is generally considered to be required for cold-induced nonshivering thermogenesis. Here, we show that mice lacking BAT Comparative Gene Identification-58 (CGI-58), a lipolytic activator essential for the stimulated LD lipolysis, have normal thermogenic capacity and are not cold sensitive. Relative to littermate controls, these animals had higher body temperatures when they were provided food during cold exposure.
<>The increase in body temperature in the fed, cold-exposed knockout mice was associated with increased energy expenditure and with increased sympathetic innervation and browning of white adipose tissue (WAT). Mice lacking CGI-58 in both BAT and WAT were cold sensitive, but only in the fasted state. Thus, LD lipolysis in BAT is not essential for cold-induced nonshivering thermogenesis in vivo. <>Rather, CGI-58-dependent LD lipolysis in BAT regulates WAT thermogenesis, and our data uncover an essential role of WAT lipolysis in fueling thermogenesis during fasting."[255.2]

[A] Hypothermia reduces angiogenesis, but this is not necessarily a bad thing as you will soon learn.

"<>Aim: Visual loss in age-related macular degeneration usually develops secondary to choroidal neovascularisation. Vascular endothelial growth factor (VEGF) is a critical regulator of retinal angiogenesis and vascular permeability, especially in hypoxic conditions. We hypothesise that hypothermia may reduce the retinal pigment epithelium (RPE) metabolism and, consequently, the levels of VEGF secretion by cultured RPE cells under hypoxic conditions. The effects of hypothermia were compared with the metabolic inhibiting effects of thiopental and nicotinamide.
<>Methods: ARPE-19 cells were grown in culture for up to 5 days under normoxic (20% O(2)) and hypoxic (1% O(2)) conditions at temperatures ranging from 27°C to 40°C. For experiments with pharmacological agents, thiopental and nicotinamide were added to the media. VEGF levels in the media were measured by ELISA and cell metabolic activity was measured by a fluorescent cell metabolic assay.
<>Results: We found that hypothermia reduced ARPE-19 cell metabolism in a temperature-dependent fashion. Hypothermia also reduced ARPE-19 cell VEGF secretion in a temperature-dependent fashion. ARPE-19 cell VEGF secretion was reduced by 38% at 34°C compared with cells grown at 37°C. Conversely, ARPE-19 cell VEGF secretion was increased by 32% at 40°C compared with cells grown at 37°C. Hypoxia increased ARPE-19 cell VEGF secretion by 84% at 37°C. However, hypothermia decreased the hypoxia-induced increase of ARPE-19 cell VEGF secretion by 30%. The effect of hypothermia on ARPE-19 cell VEGF secretion was reversible after 4 days. In contrast to hypothermia, thiopental and nicotinamide were able to reduce RPE cell metabolism but not VEGF secretion.
<>Conclusion: Hypothermia decreases both VEGF secretion and cellular metabolism in ARPE-19 cells. Hypothermia also mitigates the hypoxia-induced increase in ARPE-19 cell VEGF secretion. These effects of hypothermia are potentially unique and cannot be obtained by other pharmacological agents that slow cellular metabolism."[256]

[B] Hypothermia promotes hyperplasia (due to the strong anti-inflammatory effect). This is relatively unsurprising, now that we understand how Inflammation works.

"<>The percentage of immature myofibers relative to the total number of fibers was greater in the icing group than in the sham group 28 d after injury (P = 0.026)" [256.A]

[C] Hypothermia significantly promotes autophagy in neurons and protects them against a Traumatic Brain Injury-like injury.

"<>Here, we evaluated changes in autophagy after post-traumatic brain injury (TBI) followed by moderate hypothermia in rats. Adult male Sprague-Dawley rats were randomly divided into four groups: sham injury with normothermia group (37°C); sham injury with hypothermia group (32°C); TBI with normothermia group (TNG; 37°C); and TBI with hypothermia group (THG; 32°C). Injury was induced by a fluid percussion TBI device.
<>Moderate hypothermia (32°C) was achieved by partial immersion in a water bath (0°C) under general anesthesia for 4 h. All rats were killed at 24 h after fluid percussion TBI. The ipsilateral hippocampus in all rats was analyzed with hematoxylin and eosin staining; terminal deoxynucleoitidyl transferase-mediated nick end labeling staining was used to determine cell death in ipsilateral hippocampus. Immunohistochemistry and western blotting of microtubule-associated protein light chain 3 (LC3), Beclin-1, as well as transmission electron microscopy performed to assess changes in autophagy.
<>At 24 h after TBI, the cell death index was 27.90±2.36% in TNG and 14.90±1.52% in THG. Expression level of LC3 and Beclin-1 were significantly increased after TBI and were further up-regulated after post-TBI hypothermia. Further, ultrastructural observations showed that there was a marked increase of autophagosomes and autolysosomes in ipsilateral hippocampus after post-TBI hypothermia.
<>Our data demonstrated that moderate hypothermia significantly attenuated cell death and increased autophagy in ipsilateral hippocampus after fluid percussion TBI. In conclusion, autophagy pathway may participate in the neuroprotective effect of post-TBI hypothermia."[256.B]

[D] Hypothermia paradoxically reduces autophagy in neurons after cardiac arrest, meaning glucose and oxygen deprivation to the brain, making hypothermia therapy an extremely versatile cellular protectant.

"<>Mild hypothermia is an effective therapeutic strategy to improve poor neurological outcomes in patients following cardiac arrest (CA). However, the underlying mechanism remains unclear. The aim of the study was to evaluate the effect of mild hypothermia on intracellular autophagy and mitophagy in hippocampal neurons in a rat model of CA.
<>CA was induced in Sprague-Dawley (SD) rats by asphyxia for 5 min. After successful resuscitation, the surviving rats were randomly divided into two groups, the normothermia (NT) group and the hypothermia (HT) group. Mild hypothermia (32 °C) was induced following CA for 4 h, and animals were rewarmed at a rate of 0.5 °C/h.

Neurologic deficit scores (NDS) were used to determine the status of neurological function. Cytoplasmic and mitochondrial protein from the hippocampus was extracted, and the expression of LC3B-II/I and Parkin were measured as markers of intracellular autophagy and mitophagy, respectively.
<>Of the 60 rats that underwent CA, 44 were successfully resuscitated (73 %), and 33 survived until the end of the experiment (55 %). Mild hypothermia maintained eumorphism of nuclear and mitochondrial structures and significantly improved NDS ($p < 0.05$). Expression of LC3B-II/I and Parkin in hippocampal nerve cells were significantly increased ($p < 0.05$) in the NT group relative to the control. Meanwhile, mild hypothermia reduced the level of LC3B-II/I and Parkin ($p < 0.05$) relative to the NT group. Mild hypothermia protected mitochondria and improved neurological function following CA and resuscitation after ischemia/reperfusion (I/R) injury, likely by reducing excessive autophagy and mitophagy in neurons."[256.C]

[E] Hypothermia results in both the stimulation and dysregulation of autophagy, and serum (blood level) inflammatory factor release (Caspase-3 / TNF-a) possibly explaining a part of its lipolytic method of action and making it necessary to use large amounts of antioxidants after engaging in chronic, but likely not intermittent, Hypothermia Therapy to preserve its cellular protective effects while protecting your blood cells against its potential inflammatory effects. It may be that through an early increase in autophagy and resultant decrease in autophagy that hypothermia exerts its beneficial effects on cells, as excessive autophagy can be a deleterious process. Furthermore, this hypothermia-induced serum increase in inflammatory factors may not parallel neurological increases, because hypothermia reduces metabolism i.e. it reduces cellular respiration, thus leading invariably to a reduction in ROS generation, meaning that the lipolytic effect of hypothermia may be unrelated to its neuroprotective effects.

"<>Hypothermia is a critical consequence of extreme cold exposure that increases the risk of cold-related injury and death in humans. While the initiation of cytoprotective mechanisms including the process of autophagy and the heat shock response (HSR) is crucial to cellular survival during periods of stress, age-related decrements in these systems may underlie cold-induced cellular vulnerability in older adults. Moreover, whether potential sex-related differences in autophagic regulation influence the human cold stress response remain unknown.
<>We evaluated the effect of age and sex on mechanisms of cytoprotection (autophagy and the HSR) and cellular stress (apoptotic signaling and the acute inflammatory response) during ex vivo hypothermic cooling. Venous blood samples from 20 healthy young (10 females; mean [SD]: 22 [2] years) and 20 healthy older (10 females; 66 [5] years) adults were either isolated immediately (baseline) for peripheral blood mononuclear cells (PBMCs) or exposed to water bath temperatures maintained at 37, 35, 33, 31, or 4 ◦C for 90 min before PBMC isolation. Proteins associated with autophagy, apoptosis, the HSR, and inflammation were analyzed via Western blotting.
<>Indicators of autophagic initiation and signaling (LC3, ULK1, and beclin-2) and the HSR (HSP90 and HSP70) increased when exposed to hypothermic temperatures in young

and older adults (all $p \leq 0.007$). Sex-related differences were only observed with autophagic initiation (ULK1; $p = 0.015$). However, despite increases in autophagic initiators ULK1 and beclin-2 (all $p < 0.001$), this was paralleled by autophagic dysfunction (increased p62) in all groups (all $p < 0.001$).
<>Further, apoptotic (cleaved-caspase-3) and inflammatory (IL-6 and TNF-α) signaling increased in all groups (all $p < 0.001$). We demonstrated that exposure to hypothermic conditions is associated with autophagic dysfunction, irrespective of age or sex, although there may exist innate sex-related differences in cytoprotection in response to cold exposure as evidenced through altered autophagic initiation."[256.D]

[F] Hypothermia promotes iron detoxification, reducing ROS generation to thereby extend lifespan. Similarly to EGCg, this research proves one mechanism for the pro-longevity effect of reducing our body temperature.

"<>How animals rewire cellular programs to survive cold is a fascinating problem with potential biomedical implications, ranging from emergency medicine to space travel. Studying a hibernation-like response in the free-living nematode Caenorhabditis elegans, we uncovered a regulatory axis that enhances the natural resistance of nematodes to severe cold. This axis involves conserved transcription factors, DAF-16/FoxO and PQM-1, which jointly promote cold survival by upregulating FTN-1, a protein related to mammalian ferritin heavy chain (FTH1). <>Moreover, we show that inducing expression of FTH1 also promotes cold survival of mammalian neurons, a cell type particularly sensitive to deterioration in hypothermia. Our findings in both animals and cells suggest that FTN-1/FTH1 facilitates cold survival by detoxifying ROS-generating iron species. We finally show that mimicking the effects of FTN-1/FTH1 with drugs protects neurons from cold-induced degeneration, opening a potential avenue to improved treatments of hypothermia."[256.E]

[G] Muscle cooling reduces the slow *and* fast twitch atrophy-promoting effects of chronic caffeine use. Interestingly, in slow twitch fibers cooling promotes satellite cell proliferation, meaning that as expected, Hypothermia Therapy is predominately a *slow twitch modality*.

"<>Intracellular Ca2+ concentration ([Ca2+]i) is considered important in the regulation of skeletal muscle mass. This study tested the hypothesis that chronic repeated cooling and/or caffeine ingestion would acutely increase [Ca2+]i and hypertrophy muscles potentially in a fiber-type-dependent manner.
<>Control rats and those fed caffeine were subjected to repeated bidiurnal treatments of percutaneous icing, under anesthesia, to reduce the muscle temperature below ~5°C. The predominantly fast-twitch tibialis anterior (TA) and slow-twitch soleus (SOL) muscles were evaluated after 28 days of intervention.
<>The [Ca2+]i elevating response to icing was enhanced by caffeine loading only in the SOL muscle, with the response present across a significantly higher temperature range than in the TA muscle under caffeine-loading conditions.

<>In both the TA and SOL muscles, myofiber cross-sectional area (CSA) was decreased by chronic caffeine treatment (mean reductions of 10.5% and 20.4%, respectively). However, in the TA, but not the SOL, CSA was restored by icing (+15.4 ± 4.3% vs. noniced, $P < 0.01$). In the SOL, but not TA, icing + caffeine increased myofiber number (20.5 ± 6.7%, $P < 0.05$) and satellite cell density (2.5 ± 0.3-fold) in cross sections.
<>These contrasting muscle responses to cooling and caffeine may reflect fiber-type-specific [Ca2+]i responses and/or differential responses to elevated [Ca2+]i."[256.E2]

Molecular Hydrogen (H2) Therapy

Hydrogen is an element essential to biological life, being a component of water molecules, and involved in ATP production, and a future clean energy (Hydrogen Engines). Molecular Hydrogen Therapy, especially Hydrogen Gas Inhalation Therapy, is a future method to treat physiological decline due to its high safety profile and strong antioxidant effects[A].

Hydrogen as an antioxidant is being popularized as "Hydrogen-infused Water", made possible through special water bottle technology that decomposes H2O molecules through electrolysis (electricity) into Hydrogen Gas. Unfortunately, I do not believe a small handheld device is capable of producing enough hydrogen gas to cause a significant systemic effect in the body, considering gases tend to escape liquid confinement, regardless Hydrogen-infused water may still influence the gut microbiota positively[D]. As for Hydrogen tablets, or capsules, they are useless supplements in my humble opinion and likely to be scam products. Inhaled Hydrogen on the other hand is a proven, potent, and valuable form of Molecular Hydrogen therapy that is capable of protecting the brain and body from prooxidants[B-C].

[A] "<>Molecular hydrogen (H2) was believed to be inert and nonfunctional in mammalian cells. We overturned this concept by demonstrating that H2 reacts with highly reactive oxidants such as hydroxyl radical and peroxynitrite inside cells. H2 has several advantages exhibiting marked effects for medical applications: it is mild enough neither to disturb metabolic redox reactions nor to affect signaling by reactive oxygen species. Therefore, it should have no or little adverse effects. H2 can be monitored with an H2-specific electrode or by gas chromatography. H2 rapidly diffuses into tissues and cells to exhibit efficient effects. Thus, we proposed the potential of H2 for preventive and therapeutic applications.
<>There are several methods to ingest or consume H2: inhaling H2 gas, drinking H2-dissolved water (H2-water), injecting H2-dissolved saline (H2-saline), taking an H2 bath, or dropping H2-saline onto the eyes. Recent publications revealed that, in addition to the direct neutralization of highly reactive oxidants, H2 indirectly reduces oxidative stress by regulating the expression of various genes.
<>Moreover, by regulating gene expression, H2 functions as an anti-inflammatory, antiallergic, and antiapoptotic molecule, and stimulates energy metabolism. In addition to growing evidence obtained by model animal experiments, extensive clinical examinations were performed or are under way. Since most drugs specifically act on their specific

targets, H2 seems to differ from conventional pharmaceutical drugs. Owing to its great efficacy and lack of adverse effects, H2 has potential for clinical applications for many diseases."[256.1]

[B] Inhaled Hydrogen Therapy protects the heart from injury by increasing AMPK and mTOR. Remember that cardiac fibrosis generally coincides with cellular aging.

"<>Aims: Doxorubicin is a drug widely used in clinical cancer treatment, but severe cardiotoxicity limits its clinical application. Autophagy disorder is an important factor in the mechanism of doxorubicin-induced cardiac injury. As the smallest molecule in nature, hydrogen has various biological effects such as anti-oxidation, anti-apoptosis and regulation of autophagy. Hydrogen therapy is currently considered to be an emerging therapeutic method, but the effect and mechanism of hydrogen on doxorubicin-induced myocardial injury have not been determined. The purpose of this study was to investigate the protective effect of hydrogen inhalation on doxorubicin-induced chronic myocardial injury and its effect and mechanism on autophagy.
<>Methods: In this study, we established a chronic heart injury model by intraperitoneal injection of doxorubicin in rats for 30 days, accumulating 20 mg/kg. The effect of hydrogen inhalation on the cardiac function in rats was explored by echocardiography, Elisa, and H&E staining. To clarify the influence of autophagy, we detected the expression of LC3 and related autophagy proteins in vivo and in vitro by immunofluorescence and western blot. In order to further explore the mechanism of autophagy, we added pathway inhibitors and used western blot to preliminarily investigate the protective effect of hydrogen inhalation on myocardial injury caused by doxorubicin.
<>Results: Hydrogen inhalation can improve doxorubicin-induced cardiac function decline and pathological structural abnormalities in rats. It was confirmed by immunofluorescence that hydrogen treatment could restore the expression of autophagy marker protein LC3 (microtubule-associated protein 1 light chain 3) in cardiomyocytes reduced by doxorubicin, while reducing cardiomyocyte apoptosis. Mechanistically, Western blot results consistently showed that hydrogen treatment up-regulated the ratio of p-AMPK (phosphorylated AMP-dependent protein kinase) to AMPK and down-regulated p-mTOR (phosphorylated mammalian target of rapamycin) and mTOR ratio.
<>Conclusions: These results suggest that hydrogen inhalation can activate autophagy through the AMPK/mTOR pathway and protect against myocardial injury induced by doxorubicin. Hydrogen inhalation therapy may be a potential treatment for doxorubicin-induced myocardial injury."[256.1.2]

[C] 6h of Hydrogen Therapy per day at a dosage of 2-Liters per minute counteracts the neurological damage and behavioral deficits associated with blast-induced traumatic brain injury. This study is a forerunner to Hydrogen Therapy being utilized in Major Depression or PTSD patients to reduce neurological degeneration, and it will be a much safer and more effective therapy compared to those involving the neurotoxin Ketamine.

“<>Abstract: Detonation of explosive devices creates blast waves, which can injure brains even in the absence of external injuries. Among these, blast-induced mild traumatic brain injury (bmTBI) is increasing in military populations, such as in the wars in Afghanistan, Iraq, and Syria. Although the clinical presentation of bmTBI is not precisely defined, it is frequently associated with psycho-neurological deficits and usually manifests in the form of poly-trauma including psychiatric morbidity and cognitive disruption. Although the underlying mechanisms of bmTBI are largely unknown, some studies suggested that bmTBI is associated with blood-brain barrier disruption, oxidative stress, and edema in the brain. The present study investigated the effects of novel antioxidant, molecular hydrogen gas, on bmTBI using a laboratory-scale shock tube model in mice. Hydrogen gas has a strong prospect for clinical use due to easy preparation, low-cost, and no side effects. The administration of hydrogen gas significantly attenuated the behavioral deficits observed in our bmTBI model, suggesting that hydrogen application might be a strong therapeutic method for treatment of bmTBI.”
“<>Study Snippet 1: Although the brain is quite sensitive to ROS [Superoxide], it is secured by the BBB. Thus, disruption of BBB may result in elevated oxidative stress in the brain. In addition, several studies have reported that excessive ROS are generated in rodent models of bmTBI. Thus, we evaluated ROS formation at the somatosensory cortex in the dorsolateral part of neocortex by hydroethidine histochemistry 2 days after blast exposure and found that much greater ROS were induced by blast exposure compared with sham controls. In contrast, ROS were significantly reduced in mice exposed to hydrogen after blast exposure compared with blast alone. A 1-way ANOVA confirmed these differences ($F = 7.69$, $p = 0.005$). These results indicated that the blast exposure in this model induced oxidative stress in the brains and that hydrogen inhalation mitigates this effect”
“<>Study Snippet 2: Mice are a social species and exhibit social interaction behaviors. The sociability test has been used to investigate the preference for another mouse (social) versus an inanimate (stuffed mouse) target. Mice exposed to blast exhibited decreased time spent interacting with a social target compared with sham controls. On the other hand, mice administered hydrogen after blast exposure exhibited a similar interacting time with a social target as sham controls. A 1-way ANOVA confirmed these differences ($F = 5.02$, $p = 0.014$). Moreover, mice exposed to blast exhibited a significant increase in the time interacting with an inanimate target compared with the sham group, while mice administered hydrogen after blast exposure exhibited similar interacting time to sham controls (1-way ANOVA, $F = 5.06$, $p = 0.013$).”
“<>Study Snippet 3: To investigate whether blast exposure induces a depression-like symptom, mice underwent the tail suspension test, a widely used method for assessing depression-like symptoms. In this test, the latency to the first bout of immobility and the total time spent immobile during the 6-minute trial were evaluated. Mice exposed to blast exhibited a significant decrease in the latency to the first immobility bout compared with sham controls, indicating increased depression-like symptoms by blast exposure. However, mice administered hydrogen after blast exposure exhibited latencies comparable to sham controls. A 1-way ANOVA confirmed these differences ($F = 6.42$, $p = 0.0051$). Moreover, mice exposed to blast exhibited a significant increase in the

immobility time compared with sham controls, while mice administered hydrogen exhibited a comparable immobility time to sham controls (1-way ANOVA, $F = 6.94$, $p = 0.0036$)."
"<>Study Snippet 4: To confirm further the increased depression-like symptoms following exposure to blast wave, mice were also evaluated using the forced swim test, another assay for assessing depression-like symptoms. Mice exposed to blast waves exhibited a significant decrease in the active swimming time compared with sham controls, while mice administered hydrogen exhibited similar immobility time to sham controls (1-way ANOVA, $F = 5.95$, $p = 0.059$). Moreover, mice exposed to blast waves exhibited a significant increase in floating (immobility) time compared with sham controls, while mice administered hydrogen exhibited similar immobility time to sham controls (1-way ANOVA, $F = 11.52$, $p < 0.0001$). These results indicated that hydrogen administration ameliorates depression-like symptoms induced by blast exposure."[256.1.3]

[D] In comparing Hydrogen water (HRW) supplementation and Hydrogen gas inhalation (HI), HI was shown to significantly decrease body weight, increase Lachnospiraceae (The Family of Blautia) [See: Probiotics: Amazake] whereas HRW was shown to positively affect gut microbiota by reducing Bacteroides, and promote the growth of Lactobacillaceae bacteria. We must wonder how soon it will be before Energy Drinks incorporate Hydrogen into their propriety ingredients list.

"<>To determine the effects of hydrogen intervention on metabolic function, we conducted another study using metabolic cages to measure 24-h voluntary intake and excretions of rats during the first month of hydrogen intervention. Compared with the control group, both HRW and HI had no significant effect on the BW of rats during the four weeks, however, the BW was significantly lower at the first (263.29 ± 19.98 g vs. 296.56 ± 19.69 g, $p = 0.012$) and the fourth week (383.21 ± 29.36 g vs. 428.81 ± 31.21 g, $p = 0.024$) after HI. Compared with HRW group, the BW of rats in HI group was lower with a marginal significance ($p = 0.063$) during the four weeks. HI induced a significant decrease in both food intake ($p < 0.0001$) and water intake ($p < 0.0001$), while no reduction was observed in HRW group. During the four weeks, the defecation and urination also markedly decreased in HI group, while no effect was observed in HRW group. Spearman's correlation analysis revealed that the reduced defecation of rats in HI group was positively related to the reduction of food intake ($r = 0.43$, $p = 0.006$), and the decreased urinate was also positively related to the reduced water intake ($r = 0.64$, $p < 0.0001$)."
↓ continued
"<>In our study, HRW intake induced significant increase in the proportion of Lactobacillus, Ruminococcus, Clostridium XI, Elusimicrobium, Barnesiella, and Aquabacterium, and decrease in Bacteroides, Anaerotruncus, Desulfovibrio, Mucispirillum, and Bifidobacterium. Lactobacillus and Bifidobacterium are the most common probiotic bacteria with the reported beneficial effects including aid digestion, reduce constipation, resist infections, prevent traveler's diarrhea and ameliorate intestinal

bowel disease (IBD). In our study, HRW intake induced a significant increase in the abundance of Lactobacillus. The increased abundance of Lactobacillus induced by HRW intake may contribute to the beneficial effects of HRW."
"Compared with HRW group, the changes in fecal microbiota were found to be much less in HI group. Among these changed genera, the abundances of Blautia and Paraprevotella were significantly increased. Blautia has been considered as a probiotic bacterium that occur widely in mammalian feces and intestines. The increased abundances of Blautia may contributed to the effects of HI."
↓ Continued (DM = Differential Metabolite)
"<>Unlike HRW intake, HI had an up-regulatory effects on plasma DMs. Six of those DMs, including l-citrulline, l-leucine, sarcosine, l-glutamic acid, N-carbamoyl-l-aspartic acid, and NAAG, were belong to amino acids and their derivatives. Among them, the plasma levels of l-citrulline showed the most considerable increase in HI group compared to the controls. It has been shown in rats that only the intestine produced circulating citrulline, and the increased citrulline levels may be caused by either increased production or decreased utilization. The decreased utilization could arise from a decrease in clearance, i.e. renal failure. However, no significant change of creatinine plasma levels was observed in our study, indicating that the increased citrulline levels was not caused by the impairment of renal function. Previous study showed that the increase in plasma citrulline was correlated with protein absorption improvement in patients with short bowel syndrome (SBS) followed in the first year after resection. We supposed that the increased citrulline plasma levels may be associated with the improvement of enterocyte function, although this need to be further investigated.
↓ continued
<>HI also induced a significant increase in NAAG plasma levels. NAAG is the most prevalent and widely distributed dipeptide in the mammalian nervous system30. The levels of NAAG in plasma and cerebrospinal fluid (CSF) were much lower than those in brain tissues31. It is well established that the increase in NAAG is neuroprotective against N-methyl-d-aspartate (NMDA) receptor-mediated neurotoxicity, including ischemic brain injury. HI was first reported to exert neuroprotective effects on ischemic stroke, and further studies also found its protective effects on other neurological impairment, including traumatic brain injury, subarachnoid hemorrhage, and neurodegenerative diseases. Consistent with our results, the HI induced increase in NAAG was also observed in cortex tissues of mice with ischemic stroke. Although the ability of molecular hydrogen to scavenge hydroxyl radicals may partly explain its neuroprotective effects, the regulatory effects on NAAG may also be responsible for its protective benefits.
<>In addition, the significant increase in plasma levels of two citric acid cycle intermediates, cis-aconitic acid and malic acid, were also observed in our study, indicating that HI may accelerate mitochondrial energy metabolism. N-carbamoyl-l-aspartic acid and inosine are intermediates of pyrimidine and purine metabolism, respectively."[256.1.4] [Truncated]

Pro-Inflammation (Angiogenic) Cycle Supplementation

"That which does not kill us makes us stronger."
Twilight of the Idols: Aphorism 8: Friedrich Nietzsche

Preface: Remember, never exceed four months of essential nutrient deprivation. If you do intend on remaining on a Pro-Cycle for longer periods of time, try microdosing essential nutrients every day, or week, to avoid severe deficiencies.

Nicotine: Low POP

Another paradoxical chemical, I'm including this in the Pro-Cycle as the essential mind-altering drug, and as the replacement for Caffeine. Although it reduces IL-6, the point of its use is to promote angiogenesis. I don't consider it to be more addictive than caffeine, alcohol, or THC as they all stimulate dopamine release. When you train with high loads, consider not using Nicotine / EtOH during those weeks or months, to preserve IL-6 function and IL-6 release.

When I refer to "Nicotine" I am not advocating Cigarette use, as that habit will destroy endothelial cells to a similar degree as certain *vector vaccines*. I am instead referring to Nicotine Replacement Therapy such as Lozenges, Patches, Gums, Pouches, and even Nicotine-dipped Toothpicks.

Humorously, if you claim to hate Nicotine but love eating Tomatoes and Potatoes, you are in fact microdosing Nicotine, as they both are from the Solanaceae (Nightshade) family of plants, selfsame to Nicotiana (Tobacco) plants.

As a warning, one should cycle on and off Nicotine every One-Two Weeks of use, as one week of withdrawal is suggested for muscle nAChR resensitization, while three weeks of withdrawal is suggested to allow your brain nAChRs to resensitize completely, and the mesolimbic dopaminergic system to recalibrate.

Although the early myogenic effects of Nicotine may subside after one week of use, the angiogenic effects of Nicotine likely will persist even when the nAChR's are desensitized, depending on if the concentrations of this chemical are elevated significantly in the body, but this not ideal because you will overwhelm the brain with ROS and destroy a vast number of neurites.

In terms of combatting withdrawal symptoms such as decreased cognition, increased moodiness, or cravings, firstly and most importantly you should incorporate more moderate-high intensity cardio (average 120BPM+) into the following week(s) after your withdrawal, and secondly Agmatine is a nAChR antagonist[J] and generally not antiangiogenic, L-Theanine has been shown to reduce Nicotine withdrawal symptoms by decreasing the upregulation in nAChRs[K], and Linalool too[L]. Switching to an Anti-Inflammation Cycle immediately after beginning your withdrawal of Nicotine, and exchanging Nicotine for Caffeine + L-Theanine aligns perfectly with IMCycling, that is unless you have a strong constitution and can immediately move to an EtOH-based Pro-

Cycle. Finally, I suggest that if you do choose to use Nicotine, you sip L-Ornithine in your chosen drink all day, to counteract nicotine-induced cortisol secretion and thereby reduce a portion of its neurotoxicity[256.2].

If you intend on using Nicotine with alcohol remember the gastrointestinal interaction (Nicotine reduces Alcohol absorption).

Finally, it is my experience and suggestion that it is unwise to combine Nicotine with serious forms of Occlusion Training (especially IOTraining), or intense Hyperthermia Therapy, unless you do so for very short periods of time, such as during programmed overtraining. Also, those who use Nicotine must accommodate their cardiovascular training by adding **10 BPM** to all of their programmed steady-state or interval training intensity targeted ranges (low, moderate, high), and ensure **the majority of their weekly cardio workouts are Moderate Intensity, and their weekly cardio sessions are performed at a high frequency (4-6 Days)**, as Nicotine will superficially increase resting and exercised heart rate (due to increased blood pressure) giving the illusion of increased cardiovascular intensity, and because Nicotine may damage the cardiovascular system it is important to increase all-around cardiovascular intensity, luckily due to the potentiated muscle angiogenesis no injuries or muscle atrophy should hypothetically occur during this light overtraining. Clearly, if you skip cardiovascular exercise, then you should not use Nicotine. Refer to Thiamine at the end of this section to learn how you can protect your brain cells without inhibiting angiogenesis.

[A] Nicotine is highly angiogenic.

"<>Twenty-four hours after surgery, nicotine (0.05 microg/kg) or nicotine (0.05 microg/kg) and hexamethonium (6 mg/kg) was administered daily by intramuscular injection for 3 weeks in nicotine and nicotine-hex groups, respectively. Sham and control rabbits received an identical volume of phosphate-buffered saline injection, but without nicotine or hexamethonium. VEGF protein expression and intimal cell proliferation in balloon-injured aortas were determined by enzyme-link immunosorbent assay, immunohistochemistry, and Western blot analysis. Six rabbits died during the experiment. The remaining 42 rabbits were included in the study. VEGF protein expression in nicotine group was significantly higher than that in control group ($P < 0.01$)."[257]

[A2] Nicotine is angiogenic in skeletal muscle cells and counteracts muscle atrophy.

“<>We have recently identified that donepezil, an anti-Alzheimer drug, accelerates angiogenesis in a murine hindlimb ischemia (HLI) model. However, the precise mechanisms are yet to be fully elucidated, particularly whether the effects are derived from endothelial cells alone or from other nonvascular cells. Further investigation of the HLI model revealed that nicotine accelerated angiogenesis by activation of vascular endothelial cell growth factor (VEGF) synthesis through nicotinic receptors in myogenic cells, that is, satellite cells, in vivo and upregulated the expression of angiogenic factors, for example, VEGF and fibroblast growth factor 2, in vitro. As a result, nicotine

prevented skeletal muscle from ischemia-induced muscle atrophy and upregulated myosin heavy chain expression in vitro. The in vivo anti-atrophy effect of nicotine on muscle was also observed in galantamine, another anti-Alzheimer drug, playing as an allosteric potentiating ligand. Such effects of nicotine were attenuated in α7 nicotinic receptor knockout mice. In contrast, PNU282987, an α7 nicotinic receptor agonist, comparably salvaged skeletal muscle, which was affected by HLI. These results suggest that cholinergic signals also target myogenic cells and have inhibiting roles in muscle loss by ischemia-induced muscle atrophy."[257.1]

[B] Nicotine promotes myogenic differentiation. This does mean that Nicotine will promote Secondary Hypertrophy, but I do not believe in training infrequently while under the influence of Inflammatory compounds except for if ARCS is pursued.

"<>Thus, in the present study, we examined the effects of nicotine on the differentiation of C2C12 myoblasts in vitro and on skeletal muscle regeneration in obese mice in vivo. The results showed that nicotine promoted C2C12 myoblast differentiation by upregulating myogenic regulatory factors, including MyoD and Myogenin. Nicotine also activated the PI3K/Akt signaling pathway, while blocking PI3K with the inhibitor LY294002 abrogated the effects of nicotine on the differentiation of C2C12 cells. <>Furthermore, nicotine was injected into the cardiotoxin (CTX)-injured skeletal muscles of obese mice. The results showed that the skeletal muscles injected with nicotine regenerated more quickly than the skeletal muscles injected with saline. Taken together, our data suggested that nicotine promoted the differentiation of C2C12 cells through activation of the PI3K/Akt pathway and rescued the impaired skeletal muscle regeneration in obese mice."[258]

[C] Early Nicotine exposure facilitates memory through activating the Dopamine-1 Receptors, not through bDNF expression. Importantly, chronic and extended use of Nicotine is liable to cause reduced D1 receptor binding, which will cause one to become moody, or apathetic, it is therefore not a good idea to use chronic amounts of Nicotine for longer than a month for this reason, and also because of the excessive production of ROS.

"<>Nicotine is a highly addictive drug and exerts its effect partially through causing dopamine release, thereby increasing intrasynaptic dopamine levels in the brain reward systems. Dopaine D1 receptor (DRD1) mRNAs and receptors are localized in reward-related brain regions, which receive cholinergic input. The aim of this study is to evaluate whether nicotine administration affects the expression of DRD1s, and if so, whether epigenetic mechanisms, such as histone acetylation, are involved. Twenty Male Sprague Dawley rats received nicotine (0.4 mg/kg/day, s.c.) or saline injections for 15 days. After nicotine/saline treatment, rats were perfused with saline; prefrontal cortex (PFC), corpus striatum (STR), and ventral tegmental area (VTA) were dissected. Homogenates were divided into two parts for total RNA isolation and histone H4 acetylation studies. DRD1 mRNA expression was significantly higher in the PFC of the nicotine-treated group compared with controls; similar trends were observed in the VTA and STR. To study

epigenetic regulation, the 2kb upstream region of the DRD1 gene promoter was investigated for histone H4 acetylation in PFC samples. After chromatin immunoprecipitation with anti-acetyl histone H4 antibody, we found an increase in histone acetylation by two different primer pairs which amplified the -1365 to -1202 ($P < 0.005$) and -170 to +12 ($P < 0.05$) upstream regions of the DRD1 promoter. <>Our results suggest that intermittent subcutaneous nicotine administration increases the expression of DRD1 mRNA in the PFC of rats, and this increase may be due to changes in histone H4 acetylation of the 2kb promoter of the DRD1 gene."[259]

[C2] An elaboration on the PFC D1 receptors.

"<>The prefrontal cortex (PFC) is essential for working memory, which is the ability to transiently hold and manipulate information necessary for generating forthcoming action. PFC neurons actively encode working memory information via sustained firing patterns. Dopamine via D1 receptors potently modulates sustained activity of PFC neurons and performance in working memory tasks. In vitro patch-clamp data have revealed many different cellular actions of dopamine on PFC neurons and synapses. These effects were simulated using realistic networks of recurrently connected assemblies of PFC neurons. Simulated D1-mediated modulation led to a deepening and widening of the basins of attraction of high (working memory) activity states of the network, while at the same time background activity was depressed. As a result, self-sustained activity was more robust to distracting stimuli and noise. In this manner, D1 receptor stimulation might regulate the extent to which PFC network activity is focused on a particular goal state versus being open to new goals or information unrelated to the current goal."[260]

[D] Chronic Nicotine enhances bDNF after seven days of chronic use, although I do not believe this equates to improved intelligence when nicotine is used in *chronically high concentrations* as dopamine burnout begins to occur rapidly from the first week onward and excitotoxicity is liable to occur. In low dosages over long periods of time such as during the habit of cigarette smoking (not chain smoking), the blood level of nicotine will remain low-moderate, but during vaping, dip, or nicotine pouch use the blood level of nicotine will rise to toxic levels. It is important to understand that Nicotine enhances cognition primarily through angiogenesis and the Dopamine-1 receptors, not through bDNF.

“<>Acute nicotine administration (0.5 mg/kg i.p.) significantly decreased BDNF mRNA levels in dentate gyrus, CA3 and CA1 subfields of the rat hippocampus 2 h and 24 h after administration. However, with 7 days nicotine treatment, tolerance developed to the inhibitory effect of nicotine on BDNF mRNA expression and there was a significant increase in BDNF expression 2 h after the final injection in the CA1 region. These data suggests that changes in expression of hippocampal BDNF may be involved in the behavioral effects of nicotine observed after acute and chronic treatment.”[261]

[E] Nicotine exerts an anti-estrogenic effect in the brain, which explains why female smokers have a more "masculine" personality.

"<>Epidemiologic studies suggest that women who smoke have lower endogenous estrogen than nonsmokers. To explore the possible link between cigarette smoking and decreased endogenous estrogens, we have examined the effects of constituents of tobacco on estrogen production in human choriocarcinoma cells and term placental microsomes. In choriocarcinoma cell cultures, nicotine, cotinine (a major metabolite of nicotine), and anabasine (a minor component of cigarette tobacco) all inhibited androstenedione conversion to estrogen in a dose-dependent fashion. Removal of nicotine, cotinine, and anabasine from the culture medium resulted in the complete reversal of the inhibition of aromatase. In the choriocarcinoma cell cultures, a supraphysiologic concentration of androstenedione (73 microM) in the culture medium blocked the inhibition of aromatase caused by nicotine, cotinine, and anabasine. In preparations of term placental microsomes, nicotine, cotinine, and anabasine inhibited the conversion of testosterone to estrogen. Kinetic analysis demonstrated the inhibition to be competitive with respect to the substrate. These findings suggest that some nicotinic alkaloids directly inhibit aromatase. This mechanism may explain, in part, the decreased estrogen observed in women who smoke."[262]

[F] Nicotine activates AMPKa2 isoform expression in adipose tissue which promotes the inflammatory degradation of an Insulin receptor, leading to lipolysis and substrate competition-induced insulin resistance. This means that Nicotine use should rarely, if ever, be paired with a high carbohydrate diet, beyond the enhanced generation ROS, insulin resistance and resultant dietary-induced hyperglycemia are dangers to consider.

"<>Cigarette smoking promotes body weight reduction in humans while paradoxically also promoting insulin resistance (IR) and hyperinsulinemia. The mechanisms behind these effects of smoking are unclear. Here, we show that nicotine, a major constitute of cigarette smoke, selectively activates AMP-activated protein kinase α2 (AMPKα2) in adipocytes, which, in turn, phosphorylates MAP kinase phosphatase-1 (MKP1) at serine 334, initiating a proteasome-dependent degradation of this latter protein.
<>The nicotine-dependent reduction in MKP1 induces the aberrant activation of p38 mitogen-activated protein kinase and c-Jun amino-terminal kinase leading to increased phosphorylation of insulin receptor substrate 1 (IRS1) at serine 307. This phosphorylation of IRS1 leads to its degradation, Akt inhibition, and the loss of insulin-mediated inhibition of lipolysis. Consequently, nicotine increases lipolysis, which results in body weight reduction, but this increase also elevates the levels of circulating free fatty acids and thus causes IR in insulin-sensitive tissues.
<>These results newly place AMPKα2 as an essential mediator of nicotine-induced whole-body IR in spite of reductions in adiposity."[262.1]

[G] Nicotine although being inflammatory is neuroprotective, at the cost of reduced neuronal differentiation.

"<>Although nicotine is now well recognized as a developmental neurotoxicant, it also may have neuroprotectant properties. In the current study, we used PC12 cells to characterize the specific developmental phases in which these effects are expressed. In undifferentiated cells, nicotine had a modest effect on DNA synthesis (10% reduction), which was nevertheless selective, as no significant reductions were seen for RNA or protein synthesis. The effects were blocked by mecamylamine, indicating mediation by nicotinic acetylcholine receptors. Initiation of differentiation with nerve growth factor, which greatly increases the receptor concentration, produced a commensurate increase in the sensitivity of DNA synthesis to nicotine, while RNA and protein synthesis again remained unaffected. The organophosphate insecticide, chlorpyrifos, also interferes with DNA synthesis in undifferentiated PC12 cells, but by mechanisms independent of nicotinic receptors.
<>Accordingly, the effects of a combination of nicotine and chlorpyrifos should be additive. However, simultaneous exposure of undifferentiated cells to both agents produced less-than-additive effects at low concentrations of chlorpyrifos, and at high chlorpyrifos concentrations, nicotine produced outright protection: the combination of nicotine and chlorpyrifos had lesser effects than chlorpyrifos alone. The same neuroprotection was seen when cells were exposed to nicotine for 24 h, washed free of the drug for 24 h, and then exposed to chlorpyrifos. The results indicate that nicotine interferes with neural cell replication, with peak effects in early stages of differentiation. At the same time, nicotine promotes trophic actions that protect against neurotoxicants that work through other mechanisms." [263]
[H] Nicotine is toxic to neurites.

"<>The α7 nicotinic acetylcholine receptor (nAChR) is a ligand-gated ion channel that plays an important role in cellular calcium signaling contributing to synaptic development and plasticity and is a key drug target for the treatment of neurodegenerative conditions such as Alzheimer's disease. Here we show that α7 nAChR mediated calcium signals in differentiating PC12 cells activate the proteolytic enzyme calpain leading to spectrin breakdown, microtubule retraction, and attenuation in neurite growth. Imaging in growth cones confirms that α7 activation decreases EB3 comet motility in a calcium dependent manner as demonstrated by the ability of α7 nAChR, ryanodine, or IP3 receptor antagonists to block the effect of α7 nAChR on growth. α7 nAChR mediated EB3 comet motility, spectrin breakdown, and neurite growth was also inhibited by the addition of the selective calpain blocker calpeptin and attenuated by the expression of an α7 subunit unable to bind Gαq and activate calcium store release. The findings indicate that α7 nAChRs regulate cytoskeletal dynamics through local calcium signals for calpain protease activity."[264]

[I] Nicotine withdrawal requires ten days or more to resensitize the Nicotinic Acetylcholine Receptors. Important information for those who wish to experience the

strongest myogenic / psychological effects of the nACHR's by cycling on and off of this drug. I suggest never using Nicotine concurrently for more than two weeks.

"<>Nicotinic acetylcholine receptors (nAChRs) are of great interest because they are implicated in various brain functions. They also are thought to play an important role in nicotine addiction of smokers. Chronic (−)-nicotine, a nAChR agonist, treatment in mice and rats elicits a dose-dependent increase in nAChRs in the brain. Upregulation of nAChRs in postmortem human brains of smokers has also been reported. However, changes in nAChRs after cigarette smoking cessation in humans are poorly understood. The aim of this study was to detect the dynamic changes of nAChRs after smoking and smoking cessation in the brains of living subjects.
<>Methods: We performed 5-123I-iodo-A-85380 (123I-5IA) SPECT on nonsmokers and smokers (n = 16) who had quit smoking for 4 h, 10 d, and 21 d and calculated and compared distribution volumes (Vt) of 123I-5IA.
<>Results: The binding potential of nAChRs (Vt of 123I-5IA) in the brains of smokers decreased by 33.5% ± 10.5% after 4 h of smoking cessation, increased by 25.7% ± 9.2% after 10 d of smoking cessation, and decreased to the level of nonsmokers after 21 d of smoking cessation.
<>Conclusion: Because the upregulation of the nAChRs of the smokers after chronic exposure of the nicotine was downregulated to the nonsmokers' level by around 21 d after smoking cessation, the upregulation is a temporary effect. The decrease in nicotinic receptors to nonsmoker levels may be the breaking point during the nicotine withdrawal period."[265]

[J] Nicotine reduces Alcohol absorption, making the combinatory use of the compounds pointless, especially for very Low-Dose Alcohol use.

"<>Background: In spite of the fact that drinking and smoking often occur together, little is known about the pharmacokinetic interaction between alcohol and nicotine. Previous research in neonatal rats demonstrated that nicotine reduces blood alcohol concentrations (BACs) if alcohol and nicotine are administered simultaneously. However, it is unclear whether such a phenomenon can be observed in adult subjects, given the fact that there is an ontogenetic difference in alcohol metabolism.
<>Methods: A range of nicotine doses (0, 0.25, 0.5, 1, 2, 4, and 6 mg/kg) were administered individually with an alcohol dose (4 g/kg) via intragastric (IG) intubation to adult female rats, and the resultant BACs were measured at various time points following drug administration. Furthermore, the hypothesis that nicotine's role in reducing BACs is mediated through factors related to gastric function was examined by comparing the resultant BACs after an IG intubation or intraperitoneal (IP) injection of alcohol.
<>Results: The results from this study showed significant nicotine dose-related decreases in BACs with 0.5, 1, 2, 4, and 6 mg/kg doses of nicotine at the various time points assessed. This effect, however, occurred only when alcohol was administered via IG intubation, but not after an IP injection of alcohol.

<>Conclusions: These results suggest that the nicotine-induced decrease in BAC may be related to gastric function. One possible explanation was related to nicotine's action in delaying gastric emptying. The longer the alcohol was retained in the stomach, the more likely that the alcohol would be metabolized by gastric alcohol dehydrogenase before its absorption into the bloodstream by the small intestine (the major site of alcohol absorption).”[266]

NICOTINE WITHDRAWAL REMEMDIES (FOR AN ANTI-CYCLE)

[A] Agmatine is an antagonist of the nAChR’s.

“<>Tritiated agmatine has been used by others in ion flux methods to measure nicotinic receptor function in neurones. However, as shown here, agmatine blocks nicotinic receptor function in both the chick retina and the rat superior cervical ganglion at high concentrations.”[266.A]

[B] L-Theanine counteracts Nicotine dependence through decreasing nAChR’s, and Nicotine-stimulated dopamine production.

“<>In this study, the inhibitory effect of L-theanine, an amino acid derivative of tea, on the rewarding effects of nicotine and its underlying mechanisms of action were studied. We found that L-theanine inhibited the rewarding effects of nicotine in a conditioned place preference (CPP) model of the mouse and reduced the excitatory status induced by nicotine in SH-SY5Y cells to the same extent as the nicotine receptor inhibitor dihydro-beta-erythroidine (DHβE).
<>Further studies using high performance liquid chromatography, western blotting and immunofluorescence staining analyses showed that L-theanine significantly inhibited nicotine-induced tyrosine hydroxylase (TH) expression and dopamine production in the midbrain of mice. L-theanine treatment also reduced the upregulation of the α(4), β(2) and α(7) nicotine acetylcholine receptor (nAChR) subunits induced by nicotine in mouse brain regions that related to the dopamine reward pathway, thus decreasing the number of cells that could react to nicotine. In addition, L-theanine treatment inhibited nicotine-induced c-Fos expression in the reward circuit related areas of the mouse brain. Knockdown of c-Fos by siRNA inhibited the excitatory status of cells but not the upregulation of TH induced by nicotine in SH-SY5Y cells.
<>Overall, the present study showed that L-theanine reduced the nicotine-induced reward effects via inhibition of the nAChR-dopamine reward pathway. These results may offer new therapeutic strategies for treatment of tobacco addiction.”[266.B]

[C] Linalool counteracts Nicotine dependence, possibly through GABAergic signaling. In this study the Linalool was administered through body injection (intraperitoneal: “i.p.”), and the dosage is likely much higher than to expected through inhalation, Linalool is regardless extremely potent, even in low dosages, and at the very least inhaled Linalool

would exert synergy when combined with L-Theanine towards combatting Nicotine-withdrawal behaviors.

"<>Background: Nicotine is the addictive agent in tobacco products. The monoterpene linalool is the main ingredient in the essential oils of various aromatic plants. It has previously been demonstrated that linalool has beneficial effects on some mechanisms that are important in drug addiction.
<>Objectives: The goal of the current study was to investigate the effect of linalool on nicotine-induced conditioned place preference (CPP) in male mice.
<>Methods: CPP was induced by administering intraperitoneal (i.p.) injection of nicotine (0.5 mg/kg) during the conditioning phase. The effects of nicotinic acetylcholine receptor partial agonist varenicline and linalool on the rewarding characteristics of nicotine were tested in mice with administration of linalool (12.5, 25, and 50 mg/kg, i.p.), varenicline (2 mg/kg, i.p.) or saline 30 minutes before nicotine injection. CPP was extinguished by repeated testing, during which conditioned mice were administered varenicline and linalool every day. One day after the last extinction trial, mice that received linalool, varenicline or saline 30 minutes before a priming injection of nicotine (0.1 mg/kg, i.p.) were immediately tested for reinstatement of CPP.
<>Results: Linalool attenuated nicotine acquisition (50 mg/kg, $p < .01$) and reinstatement (25 and 50 mg/kg, respectively $p < .05$, $p < .01$) and accelerated the extinction of nicotine-induced CPP (50 mg/kg, $p < .05$). Linalool exhibited similar effects on the reference drug varenicline in the CPP phases.
<>Conclusion: These results suggest that linalool may be helpful as an adjuvant for the treatment of nicotine use disorder."[266.C]

DHEA: Moderate POP

DHEA promotes angiogenesis through activating ERK1/2, and this effect is likely to be systemic when dosed orally in human beings, considering DHEA is able to pass the Blood Brain Barrier it is an excellent nootropic that rivals Quercetin (See Anti-Inflammation Cycle Supplementation: DHEA), it should therefore be considered an essential nutrient for the brain.

"<>Dehydroepiandrosterone (DHEA) activates a plasma membrane receptor on vascular endothelial cells and phosphorylates ERK 1/2. We hypothesize that ERK1/2-dependent vascular endothelial proliferation underlies part of the beneficial vascular effect of DHEA. DHEA (0.1-10 nm) activated ERK1/2 in bovine aortic endothelial cells (BAECs) by 15 min, causing nuclear translocation of phosphorylated ERK1/2 and phosphorylation of nuclear p90 ribosomal S6 kinase. ERK1/2 phosphorylation was dependent on plasma membrane-initiated activation of Gi/o proteins and the upstream MAPK kinase because the effect was seen with albumin-conjugated DHEA and was blocked by pertussis toxin or PD098059. A 15-min incubation of BAECs with 1 nm DHEA (or albumin-conjugated DHEA) increased endothelial proliferation by 30% at 24 h.

<>This effect was not altered by inhibition of estrogen or androgen receptors or nitric oxide production. There was a similar effect of DHEA to increase endothelial migration. DHEA also increased the formation of primitive capillary tubes of BAECs in vitro in solubilized basement membrane. These rapid DHEA-induced effects were reversed by the inhibition of either Gi/o-proteins or ERK1/2. Additionally, DHEA enhanced angiogenesis in vivo in a chick embryo chorioallantoic membrane assay. These findings indicate that exposure to DHEA, at concentrations found in human blood, causes vascular endothelial proliferation by a plasma membrane-initiated activity that is Gi/o and ERK1/2 dependent. These data, along with previous findings, define an important vascular endothelial cell signaling pathway that is activated by DHEA and suggest that this steroid may play a role in vascular function."[266.0]

Echinacea Purpurea + Echinacea Angustifolia: Moderate POP

These two herbs in combined form are my favorite angiogenic supplement, and although this is ironic and paradoxical considering I have mentioned most phytochemicals inhibit or suppress angiogenesis, there are always exceptions to every rule, and this is one.

E. Purpurea and E. Angustifolia are plants that have phytochemicals called Alkylamides in them. These phytochemicals share pharmacodynamical similarity to cannabinoids in that they potently activate the Cannabinoid-2 Receptors, thus stimulating an immune reaction.

I suggest consuming them in the form of tea, until extracts become more popular. If you lack a kettle and loose-leaf tea filter, the second best brewing method is to put the leaves into the bottom of an empty coffee pot, add water, activate the brew cycle, and let the ground roots steep for ten-fifteen minutes, then use a strainer and a cup or bowl to extract the final liquid product. Consume it either intra-workout, or all day.

[A] Echinacea Purpurea promotes angiogenesis.

"<>The data from the current study revealed that treatment with Avemar or Echinacea pre- and post-infarction efficiently induced great mobilization of CD34+ cells from their niches on day 1 and 14 after AMI. On the other hand, animals that received Avemar only after infarction development exhibited no change in the mobilization of SCs, while those receiving Echinacea showed more circulating CD34+ cells on days 7 and 14 compared to their corresponding AMI values. These results revealed the importance of Avemar as a prophylactic agent and Echinacea as both a prophylactic and therapeutic agent triggering an efficient mobilization of CD34+ cells which may, in turn, contribute to regeneration of damaged myocardium.
<>Increased SC mobilization could be explained according to the established concept that, within the BM, SCs are anchored to stromal cells via integrin binding to cell adhesion molecules and via interaction with cell surface- or matrix-bound cytokines. Disruption of this interaction represents the principal underlying mechanism of several currently applied mobilization strategies including colony-stimulating factors such as G-CSF and GM-CSF.

<>Another underlying mechanism depends on increasing serum levels of growth factors which provide a gradient thus guiding SCs out into the blood, such as VEGF, erythropoietin, and IL-8. The circulating levels of SCs in case of pre- and post-treatment with Avemar or Echinacea decreased to a certain extent after 7 days and then increased significantly again after 14 days, suggesting a migration of CD34+ cells to the infarcted myocardium."[266.1]

[B] Echinacea Purpurea and Angustifolia, when combined, significantly promote angiogenesis.

"<>Echinacea is used for its immunostimulating properties and may have a role in modulating adverse immune effects of chemotherapy (i.e., use of 5-fluorouracil (5-FU); fluorouracil and its immunosuppressive effect). Patients may seek herbal remedies such as Echinacea (Echinacea angustifolia and Echinacea purpurea) for immune stimulation. Echinacea extracts have been prescribed to supplement cancer chemotherapy for their immune-supportive effects; however, the extracts may also influence tumourgenesis. <>Our study aimed to determine the proliferative effect of the ethanolic blend of E. angustifolia and E. purpurea on various cancer cervical and bile duct cell lines, including HELA and QBC-939. Various cancer cells (HeLa and QBC-939) and human vein epithelial cells (HUVEC) were treated with the Echinacea blend sample that was evaporated and reconstituted in Dimethyl sulfoxide (DMSO). As the extract concentration of Echinacea was increased from 12.5 μg/mL to 25 μg/mL, there was an increase in cell inhibition up to 100%, which then reduced to 90% over the next three concentrations, 50 μg/mL, 100 μg/mL, and 200 μg/mL, in HeLa cells; further inhibitory effects were observed in QBC-939 cells, from 9% inhibition at a concentration of 25 μg/mL up to 37.96% inhibition at 100 μg/mL concentration. <>Moreover, this is the first study to report the growth-promoting effects of this Echinacea blend in HUVEC, up to **800%** at a dose concentration of 200 μg/mL. Previous studies have suggested that chicoric acid of Echinacea spp. is responsible for the increased cell growth. The results of this study show that the hydroethanolic extract of Echinacea herbal medicine promotes the growth of HeLa cells and QBC-939 cancer cell proliferation, and may interfere with cancer treatment (i.e., chemotherapy drugs such as 5-fluorouracil and Cisplatin (DDP)). <>However, the Echinacea blend shows potential in neurodegenerative diseases with growth-promoting effects in HUVEC. Further animal trials (in vivo effect) measuring dose toxicology are necessary to demonstrate the interaction of this blend with body and tumor growth, and also any positive synergistic or adverse interaction with chemotherapeutic drugs listed, so as to confirm the current observation and epithelial tissue growth or regeneration in a neurodegenerative disease model."[266.2]

Bacillus Coagulans (Probiotic): Moderate POP

Bacillus Coagulans promotes the release of IL-6/10, making it a *pro-inflammatory* probiotic, alongside Nattō.

"<>Three observations from the current work reported here are of key importance in the validation of similar biological activities of the inactivated B. coagulans GBI-30 cells, compared to the immune-modulating properties of cell wall fractions from living BC30: 1) Both can increase the CD69 activation marker on lymphocytes, 2) both are able to increase production of the proinflammatory cytokine IL-6."[267]

Lettuce Juice: Low POP

Lettuce is low in nutrients, and contains a high level of Nitrates, making Lettuce Juice the perfect "NO Booster" to consume intra-workout, for it is not only easy to find, but relatively inexpensive globally. Conversely, someone with a death wish could buy Potassium Nitrate inexpensively and experiment with it, at a *very high risk of death* if dosed incorrectly![267.1]

Lactobacillus Rhamnosus (Probiotic): Moderate POP

Lactobacillus Rhamnosus promotes angiogenesis and reduces fibrosis.

"<>Skin wounds are an important clinical problem which affects millions of people worldwide. The search for new therapeutic approaches to improve wound healing is needed. The present study aimed to evaluate the effects of the oral treatment with the skin-related probiotics Lactobacillus johnsonii LA1 (LJ), L. paracasei ST11 (LP), and L. rhamnosus LPR (LR) in a model of excisional skin wounds in Swiss mice. The animals received daily oral gavage of PBS or 1 × 107 colony-forming units of LJ, LP, or LR, singly, beginning just after the creation of wounds until euthanasia. Blood flow was evaluated by laser Doppler perfusion imaging. Myeloperoxidase and N-acetyl-β-D-glucosaminidase activities were used to assess the accumulation of neutrophils and macrophages, respectively. The wound tissue was also collected for histological analyses (H&E, Toluidine blue, and Picrosirius red staining).
<>The macroscopic wound closure rate was faster only in mice treated with LR, but not with LJ and LP, when compared to mice treated with PBS. Histological evaluations showed that treatment with LR stimulated wound epithelization when compared to PBS. Further analyses showed that wounds from LR-treated mice presented a significant decrease in macrophage ($p < 0.001$) and mast cell ($p < 0.001$) infiltration, along with improved angiogenesis ($p < 0.001$) and blood flow ($p < 0.01$). <>Of note, collagen deposition and scarring were reduced in LR-treated mice when compared to PBS-treated mice. In conclusion, our results show that the oral treatment with Lactobacillus rhamnosus accelerates skin wound closure and reduces scar, besides to reducing inflammation and fibrogenesis and improving angiogenesis in the wounded skin."[268]

Sildenafil: High POP

This systemically angiogenic erectile dysfunction drug, formerly sold as Viagra, is now sold on Erectile Dysfunction websites without insurance required, although you will need

to be male, and get approval from the on-call telemedicine doctor that works for the Sildenafil provider, e.g. BlueChew.

[A] Sildenafil is angiogenic.

"<>cGMP-degrading pathways have received little attention in the context of angiogenesis. In the present study we set out to determine whether cGMP-specific phosphodiesterase 5 (PDE5) inhibition affects new blood vessel growth. Incubation of chicken chorioallantoic membranes (CAMs) in vivo with sildenafil increased vascular length in a dose-dependent manner. Moreover, incubation of cultured endothelial cells (ECs) with the PDE5 inhibitor promoted proliferation, migration, and organization into tube-like structures. The effects of sildenafil on the angiogenesis-related properties of EC could be blocked by pre-treatment with the soluble guanylyl cyclase (sGC) inhibitor ODQ or the protein kinase G (PKG) I inhibitor DT-3. In addition, over-expression of sGC in EC led to an enhanced growth and migratory response to sildenafil.
<>To study the signaling pathways implicated in the sildenafil-stimulated angiogenic responses we determined the phosphorylation status of mitogen-activated protein kinase (MAPK) members. Incubation of cells with sildenafil increased both extracellular signal regulated kinase 1/2 (ERK1/2) and p38 phosphorylation in a time-dependent manner. Inhibition of MEK by PD98059 and p38 with SB203580 blocked sildenafil-induced proliferation and migration, respectively, suggesting that these MAPK members are downstream of PDE5 and mediate the angiogenic effects of sildenafil. PDE5 inhibitors could, thus, be used in disease states where neo-vessel growth is desired."[269]

[B] Sildenafil promotes memory consolidation.

“<>Sildenafil (Viagra) has been introduced recently in market to correct male impotency and has gained immense popularity for its dramatic effects all over the world. The present study was designed to investigate the effect of sildenafil on learning and memory in mice using elevated plus maze. A total of XV groups of animals were employed in the present study. Central cholinergic pathways play a crucial role in learning and memory processes. Physostigmine, an anticholinesterase agent (0.5 mg, 1.0 mg kg(-1), i.p) was employed for its memory enhancing property and alprazolam a benzodiazepine receptor agonist served as a memory-impairing agent.
<>In the present study, alprazolam produced anterograde amnesia (at 0.5 mg kg(-1), i.p) and retrograde amnesia (at 0.25 mg, 0.5 mg, 0.75 mg kg(-1), i.p.) in separate groups of animals. Caffeine at 5 mg, 10 mg and 20 mg kg(-1), i.p. (an established psychostimulant) did not show any significant change in learning and memory of mice. Sildenafil (at 8 mg kg(-1), i.p.) administered 30 minutes prior to training on first day produced a marginal decrease in transfer latency time on first day; whereas, sildenafil (at 2 mg, 4 mg, 8 mg kg(-1), i.p.) administered immediately after training on first day produced a dose-dependent improvement of memory in mice. However, further studies need to be carried out to elucidate the underlying mechanism of sildenafil as a memory enhancer.”[270]

[C] Sildenafil is capable of preventing Heat Shock Protein-induced angiogenesis suppression which appears to occur through mitochondrial dysfunction (likely excessive ROS), meaning that *intense* Hyperthermia Therapy, although myogenic through IL-6 and Androgen receptor activity, may suppress skeletal muscle or neurological angiogenesis, and that Sildenafil use before Hyperthermia Therapy may prevent the anti-angiogenic effect of heat stress through the promotion of mitochondrial biogenesis. Furthermore, if Sildenafil is capable of facilitating angiogenesis in the presence of mitochondrial dysfunction, it could be considered an essential co-drug for any Pro-Cycle, including Nicotine cycles, to prevent the angiotoxicity of excessive inflammation.

"<>Akt3 regulates mitochondrial content in endothelial cells through the inhibition of PGC-1α nuclear localization and is also required for angiogenesis. However, whether there is a direct link between mitochondrial function and angiogenesis is unknown. <>Here we show that Akt3 depletion in primary endothelial cells results in decreased uncoupled oxygen consumption, increased fission, decreased membrane potential, and increased expression of the mitochondria-specific protein chaperones, HSP60 and HSP10, suggesting that Akt3 is required for mitochondrial homeostasis. Direct inhibition of mitochondrial homeostasis by the model oxidant paraquat results in decreased angiogenesis, showing a direct link between angiogenesis and mitochondrial function. <>Next, in exploring functional links to PGC-1α, the master regulator of mitochondrial biogenesis, we searched for compounds that induce this process. We found that, sildenafil, a phosphodiesterase 5 inhibitor, induced mitochondrial biogenesis as measured by increased uncoupled oxygen consumption, mitochondrial DNA content, and voltage-dependent anion channel protein expression. Sildenafil rescued the effects on mitochondria by Akt3 depletion or pharmacological inhibition and promoted angiogenesis, further supporting that mitochondrial homeostasis is required for angiogenesis. Sildenafil also induces the expression of PGC-1 family member PRC and can compensate for PGC-1α activity during mitochondrial stress by an Akt3-independent mechanism. The induction of PRC by sildenafil depends upon cAMP and the transcription factor CREB.
<>Thus, PRC can functionally substitute during Akt3 depletion for absent PGC-1α activity to restore mitochondrial homeostasis and promote angiogenesis. These findings show that mitochondrial homeostasis as controlled by the PGC family of transcriptional activators is required for angiogenic responses."[270.1]

L-Citrulline: Low POP

[A] Citrulline is anabolic by way of promoting PGC1a expression, angiogenesis, and

nitric oxide production. L-Citrulline should be dosage at a high frequency, such as pre, and post-workout, and multiple times a day if possible.

"<>Six-week-old ICR mice were orally supplemented with l-citrulline (250 mg kg−1) daily, and their performance in weight-loaded swimming exercise every other day for 15

days, was evaluated. In addition, mice muscles were weighed and evaluated for the expression of PGC-1α and PGC-1α-regulated genes.
<>Mice orally supplemented with l-citrulline had significantly higher gastrocnemius and biceps femoris muscle mass. Although not statistically significant, l-citrulline prolonged the swimming time to exhaustion. PGC-1α upregulation was associated with vascular endothelial growth factor α (VEGFα) and insulin-like growth factor 1 (IGF-1) upregulation. VEGFα and IGF-1 are important for angiogenesis and muscle growth, respectively, and are regulated by PGC-1α. Treatment with NG-nitro-l-arginine methyl ester hydrochloride (l-NAME), a nitric oxide synthesis inhibitor, suppressed the l-citrulline-induced PGC-1α upregulation in vitro."[271]

[B] Citrulline has better bioavailability as a Nitric Oxide Booster than arginine. This is important information as the overconsumption of L-Arginine may result in the increased excretion of other ergogenic chemicals, especially those found in common Pre-Workout powders.

"<>The higher activity and bioavailability of l-citrulline, compared to l-arginine, is due to several factors. For example, 0.75 grams of l-citrulline ingested twice daily (1.5 g total) increased the l-arginine area under the curve to a similar degree as ingesting 1.6 g of l-arginine twice daily (3.2 g total) (271 vs. 289 μmol·h·L−1) [12]. Orally ingested l-citrulline is absorbed by the enterocytes of the small intestine. However, the lack of gastrointestinal distress from l-citrulline compared to l-arginine supplementation may suggest that l-citrulline uptake utilizes a differing transport system."[272]

L-Arginine: Low POP

[A] Arginine magnifies training-induced angiogenesis.

"<>A Western blot analysis showed that training with L-arginine significantly increased VEGF protein expression by 2.9-fold in the soleus muscle and by 1.7-fold in the left ventricle, but the increase with training alone was insignificant. The tissue endothelial nitric oxide synthase protein levels were significantly increased in both the soleus (by 1.3-fold) and the left ventricle (by 1.4-fold) only after training with L-arginine supplementation. In the plantaris muscle, these protein levels did not change after either training or L-arginine treatment.
<>The present results suggest that in middle-aged rats, L-arginine administration caused additional effects on exercise-induced angiogenesis by presumably promoting VEGF expression in the hind-leg muscle as well as in the left ventricle."[273]

[B] Arginine is a gastrointestinal irritant making it a supplement one should singularly consume intra-workout only, especially during endurance workouts, or only post-workout.

"<>In the case of arginine, this compares with the laxative threshold of the nonabsorbed disaccharide alcohol, lactitol"[274]

Citric Acid: Low POP

[A] Citric acid is angiogenic, and potentially myogenic through activating mTOR.

"<>Upregulation of angiogenic factors such as vascular endothelial growth factor and fibroblast growth factor suggested that the effect of citrate involves modulation of expression of angiogenic growth factors. LY 294002, an inhibitor of PI3K-Akt pathway, and wortmannin, an inhibitor of Akt pathway, reversed the effect of citrate in human umbilical vein endothelial cells. Citrate induced significant upregulation and activation of Akt in endothelial cells. Rapamycin, an inhibitor of mTOR, also reversed the effect of citrate in human umbilical vein endothelial cells and sprouting of aortic rings suggesting that the angiogenic effect of citrate involves activation of PI3K-Akt-mTOR pathway."[275]

[B] Citric acid promotes adipogenesis, and glucose resistance.

"<>However, the group receiving citrate+sucrose showed augmented fasting glycaemia, glucose intolerance and the expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-10) in their AT. Therefore, our results suggest that citrate consumption contributes to increased AT inflammation and altered glucose metabolism, which is indicative of initial insulin resistance. Thus, citrate consumption could be a previously unknown causative agent for the complications associated with obesity."[276]

D-Beta-Hydroxybutyrate or Beta-Hydroxybutyrate (D-BHB / BHB): High POP

As a ketone, BHB facilitates lipolysis, with D-BHB having greater bioavailability and potency at an increased cost.

[A] BHB enhances protein synthesis.

“<>Because intravenous infusion of beta-hydroxybutyrate (beta-OHB) has been reported to decrease urinary nitrogen excretion, we investigated in vivo metabolism of leucine, an essential amino acid, using L-[1-13C]leucine as a tracer during beta-OHB infusion. Leucine flux during beta-OHB infusion did not differ from leucine flux during normal saline infusion in nine normal subjects, whereas leucine oxidation decreased 18-41% (mean = 30%) from 18.1 +/- 1.1 mumol.kg-1.h-1 (P less than 0.01), and incorporation of leucine into skeletal muscle protein increased 5-17% (mean = 10%) from 0.048 + 0.003%/h (P less than 0.02).
<>Since blood pH during beta-OHB infusion was higher than the pH during saline infusion, we performed separate experiments to study the effect of increased blood pH on leucine kinetics by infusing sodium bicarbonate intravenously. Blood pH during sodium

bicarbonate infusion was similar to that observed during the beta-OHB infusion, but bicarbonate infusion had no effect on leucine flux or leucine oxidation. <>We conclude that beta-OHB decreases leucine oxidation and promotes protein synthesis in human beings."[277]

[B] BHB is inflammatory.

"<>Scope: Cell culture studies indicate that the ketone β-hydroxybutyrate (β-OHB) directly inhibits the NLRP3 inflammasome, a key regulator of inflammation. However, direct evidence demonstrating this effect in humans is lacking.
<>Methods and results: To determine the effects of acutely raising blood β-OHB in healthy humans, two separate randomized double-blind placebo-controlled experiments are conducted using similar methods but each employed different exogenous ketone supplements. Participants' blood β-OHB is directly elevated by ketone salts (0.3 g β-OHB per kg; Study 1, N = 10 males) or ketone monoester (0.482 g β-OHB per kg; Study 2, N = 18, equal males/females). Markers of NLRP3 inflammasome activation include caspase-1, IL-1β secretion, and IL1B and NLRP3 mRNA in LPS-stimulated whole blood collected at the baseline and 30 minutes following supplementation. Caspase-1 activation increases after ketone salt (Study 1: condition × time interaction, $p = 0.012$) and monoester supplementation (Study 2: condition × time interaction, $p = 0.016$) compared to placebo. IL-1β secretion increases (main effect of condition, $p = 0.024$; Study 2) while IL1B and NLRP3 mRNA remain unchanged.
<>Conclusion: Measures of NLRP3 activation increases when blood β-OHB is elevated using ketone supplements, suggesting that increasing β-OHB exogenously may have unintended effects that augment inflammatory activation."[277.1]

L-Glutamine: Low POP

Glutamine is a very interesting amino acid; it has a rather neutral flavor making it good to add to food or drinks. It is an excellent idea to substitute a GlySer Myogenic Drink, or Glycine specifically, for a L-Glutamine-based Myogenic Drink, considering on the Pro-Cycle you should be exercising twice a day (or more), it will only further accelerate myogenesis and lipolysis if consumed chronically during the entire day, alongside a good acutely administered dosing Pre/Post-Exercise.

[A] Glutamine reduces myogenic factor activity, but Leucine seems to counteract its catabolic effects to a certain extent.

"<>This study compared the effects of leucine and glutamine on the mTOR pathway, on protein synthesis and on muscle-specific gene expression in myogenic C(2)C(12) cells. Leucine increased the phosphorylation state of mTOR, on both Ser2448 and Ser2481, and its downstream effectors, p70(S6k), S6 and 4E-BP1. By contrast, glutamine decreased the phosphorylation state of mTOR on Ser2448, p70(S6k) and 4E-BP1, but did not modify

the phosphorylation state of mTOR on Ser2481 and S6. Whilst the phosphorylation state of the mTOR pathway is usually related to protein synthesis, the incorporation of labelled methionine/cysteine was only transiently modified by leucine and was unaltered by glutamine. However, these two amino acids affected the mRNA levels of desmin, myogenin and myosin heavy chain in a time-dependant manner.
<>In conclusion, leucine and glutamine have opposite effects on the mTOR pathway. Moreover, they induce modification of muscle-specific gene expression, unrelated to their effects on the mTOR/p70(S6k) pathway."[279]

[B] Glutamine is lipolytic through activating Uncoupling Protein-2.

"<>Increased glutamine concentration to 500 or 5000 μM caused mitochondrial uncoupling in myoblasts and myotubes, decreasing the efficiency of the respiratory chain to ~70%."[280]

[B2] UCP2 prevents Insulin's cellular actions, making its activity important for lipolysis to occur in exercised, or fasted subjects, thus Glutamine is an excellent supplemented amino acid to use on a Ketogenic Diet, or low carb diet.

"<>Uncoupling protein-2 (UCP2) regulates insulin secretion by controlling ATP levels in beta-cells. Although UCP2 deficiency improves glycemic control in mice, increased expression of UCP2 interferes with glucose-stimulated insulin secretion. These observations link UCP2 to beta-cell dysfunction in type 2 diabetes with a perplexing evolutionary role. We found higher residual serum insulin levels and blunted lipid metabolic responses in fasted ucp2(-/-) mice, supporting the concept that UCP2 evolved to suppress insulin effects and to accommodate the fuel switch to fatty acids during starvation.
<>In the absence of UCP2, fasting initially promotes peripheral lipolysis and hepatic fat accumulation at less than expected rates but culminates in protracted steatosis, indicating diminished hepatic utilization and clearance of fatty acids. We conclude that UCP2-mediated control of insulin secretion is a physiologically relevant mechanism of the metabolic response to fasting."[280.1]

[B3] UCP2 promotes myogenic proliferation (hypertrophy) at the cost of myogenic differentiation (hyperplasia), making chronic Glutamine use excellent for a Pro-Inflammation Cycle, or at the very least indicating Glutamine should be used immediately after a workout to enhance myogenic proliferation. miR-133a = suppressor of UCP2.

"<>The continuous suppression of UCP2 and induction of UCP3 during myogenesis prompt the speculation that the down-regulation of UCP2 and up-regulation of UCP3 might be indispensable to myotube formation. To verify this hypothesis, a UCP2 expression plasmid designed to specially express the UCP2 open reading frame (ORF) without the miR-133a-responsive 3′-UTR was constructed. We transfected this plasmid

into C2C12 cells to rescue the suppressive effect of miR-133a on UCP2. Strikingly, miR-133a-resistant UCP2 strongly inhibited differentiation but enhanced proliferation of C2C12 cells, as indicated by the dramatic decrease of myogenin, myosin heavy chain, MyoD, MEF2, and skeletal α-actin and the marked increase of Ki-67 and proliferating cell nuclear antigen.
<>UCP2 siRNA significantly attenuated this effect of UCP2 because cells co-transfected with the UCP2 ORF and UCP2 siRNA exhibited constant levels of myogenic and proliferative markers when compared with green fluorescent protein transfected cells. In contrast, overexpression of UCP3 caused only a slight reduction of myogenic markers and had almost no effect on proliferative markers. Despite their structural and functional similarities, therefore, UCPs may play different roles in muscle cell differentiation. UCP2 may play a role at an earlier stage in the differentiation process, perhaps in maintaining the undifferentiated state and promoting myoblasts proliferation. On the other hand, miR-133a may serve to maintain and define cell types by suppressing unwanted UCP2 transcripts. Alternatively, the loss of basal UCP2 functions (e.g. mediating proton leak and controlling the production of reactive oxygen species) are compensated for by UCP3, which has a comparatively lower impact on muscle development.
<>Hence, down-regulation of UCP2 and up-regulation of miR-133a may form a checkpoint of the myoblast-myotube transition. Taken together, our findings illustrate a novel function of UCP2 in fine-tuning myogenic differentiation of muscle cells."[280.2]

[C] Glutamine enhances IL-6 release.

"<>Glutamine is also synthesized in skeletal muscle and is involved in protein synthesis within this tissue. During exercise, plasma levels of glutamine decline, and this may affect the concentration of plasma IL-6 via a decrease in IL-6 synthesis and release from muscle. We hypothesized that glutamine supplementation would attenuate the exercise-induced decrease in plasma glutamine concentration and, thus, further enhance levels of plasma IL-6.
<>Eight healthy men participated in a randomized, double-blind, crossover study in which they performed 2 h of cycle ergometry at 75% of peak O2 uptake. They received glutamine, glutamine-rich protein, or placebo supplementation at intervals during and 2 h after exercise.
<>Exercise induced an 11-fold increase in plasma IL-6, which was further enhanced by glutamine (18-fold) and glutamine-rich protein (14-fold) supplementation, administered at doses that attenuated the exercise-induced decrease in plasma glutamine concentration."[281]

[D] Glutamine counteracts Cortisol-induced upregulation of myostatin expression and muscle atrophy.

"<>Excess glucocorticoids (GCs) cause muscle atrophy. Glucocorticoid-induced muscle atrophy is associated with increased intramuscular myostatin expression. Myostatin is a negative regulator of skeletal muscle mass. Glutamine prevents GC-induced muscle

atrophy. We hypothesized that glutamine effect on reversal of GC-induced muscle atrophy is mediated in part by suppression of myostatin. We administered daily to male Sprague-Dawley rats dexamethasone, dexamethasone plus glutamine, saline or saline plus glutamine, all pair-fed. Animals were killed on day 5. Body weight and weights of gastrocnemius muscles were measured. Myostatin expression was measured by Northern and Western blots, and was compared with glyceraldehyde-3-phosphate dehydrogenase. <>Myoblast C2C12 cells were exposed to dexamethasone, or dexamethasone and glutamine, and their myostatin messenger RNA and protein expression compared with glyceraldehyde-3-phosphate dehydrogenase. Myostatin promoter activity was measured by luciferase activity of transfected C2C12 cells, grown in medium including dexamethasone, or dexamethasone plus glutamine.
<>Rats that received dexamethasone showed significant body and muscle weight loss accompanied by an increase in intramuscular myostatin expression, compared with their saline-treated controls. Pair-fed rats given dexamethasone plus glutamine had significantly less reduction in body and muscle weights and lower myostatin expression when compared with those treated with dexamethasone alone.
<>In C2C12 myoblast cells, addition of glutamine to dexamethasone prevented the hyperexpression of myostatin induced by dexamethasone. Myostatin promoter activity increased in cells exposed to dexamethasone, but this increase was partially blocked by addition of the glutamine. Administration of glutamine partially prevents GC-induced myostatin expression and muscle atrophy, providing a potential mechanism for the prevention of muscle atrophy induced by glucocorticoids."[281.1]

Taurine: Low POP

[A] Taurine is angiogenic through activating ERK.

"<>Taurine, a non-essential sulfur-containing amino acid, plays a critical role in cardiovascular functions. We here examined the effect of taurine on angiogenesis and its underlying signal pathway. Taurine treatment increased angiogenesis in vitro and in vivo, which was followed by activation of the phosphatidylinositol 3-kinase (PI3K)/Akt, MEK/ERK, and Src/FAK signaling pathways.
<>Further, taurine promoted endothelial cell cycle progression to the S and G2/M phases by up-regulating the positive cell cycle proteins, particularly cyclins D1 and B, as well as down-regulating the negative cell cycle proteins, p53 and p21(WAF1/CIP1), resulting in Rb phosphorylation. This angiogenic event was inhibited by inhibitors of PI3K and MEK. In addition, a PI3K inhibitor blocked the activation of Akt and ERK, while Akt knockdown did not affect taurine-induced ERK activation, indicating that PI3K is an upstream mediator of both MEK and Akt. <>Taurine-induced endothelial cell migration was suppressed by Src inhibitor, but not by other inhibitors, suggesting that the increase in cell migration is regulated by Src-dependent pathway.
<>Moreover, inhibition of cellular taurine uptake by β-alanine and taurine transporter knockdown promoted taurine-induced cell proliferation, ERK and Akt activation, and in vivo angiogenesis, suggesting that extracellular taurine induces angiogenesis. However,

taurine did not induce vascular inflammation and permeability in vitro and in vivo. These data demonstrate that extracellular taurine promotes angiogenesis by Akt- and ERK-dependent cell cycle progression and Src/FAK-mediated cell migration without inducing vascular inflammation, indicating that it is potential use for the treatment of vascular dysfunction-associated human diseases."[282]

[B] Taurine is toxic when administered chronically, most likely due to being a potent GABAA Receptor agonist, as the GABAArs desensitize readily over time and even begin to exert a paradoxically anxiogenic (excitatory) effect, therefore it is best administered as a supplement acutely, once per day, which would hypothetically counteract Beta-Alanine-induced endogenous Taurine depletion, and one should cycle off of it for a full week every six to eight months.

"<>Taurine is one of the most abundant nonprotein amino acids shown to be essential for the development, survival, and growth of vertebrate neurons. We previously demonstrated that chronic taurine supplementation during neonatal development results in changes in the GABAergic system. The brains of mice chronically treated with taurine have decreased levels of GABA(A)β subunits and increased expression of GAD and GABA, which contributes to hyperexcitability. This down regulation of GABA(A)receptor subunit expression and function may be due to a sustained interaction of taurine with GABA(A)receptors.
<>This desensitization decreases the efficacy of the inhibitory synapses at the postsynaptic membrane. If changes occur in the GABAergic system as a possible compensatory mechanism due to taurine administration, then it is important to study all aspects by which taurine induces hyperexcitability and affects motor behavior.
<>We therefore hypothesized that modification of the GABAergic system in response to taurine supplementation influences motor learning capacity in mice. To test this hypothesis, the rotarod task was employed after chronic taurine supplementation in drinking water (0.05% for 4 weeks). Control animals receiving no taurine supplementation were also tested in order to determine the difference in motor learning ability between groups. Each animal was trained on the rotarod apparatus for 7 days at an intermediate speed of 24 rpm in order to establish baseline performance. On the testing day, each animal was subjected to eight different predefined speeds (5, 8, 15, 20, 24, 31, 33, and 44 rpm).
<>From our observations, the animals that underwent chronic taurine supplementation appeared to have a diminished motor learning capacity in comparison to control animals. The taurine-fed mice displayed minor improvements after repeated training when compared to controls. During the testing session the taurine-fed mice also exhibited a shorter latency to fall, as the task requirements became more demanding."[283]

L-Aspartic Acid: Low POP

Aspartate promotes angiogenesis through mTORC1.

“<>Angiogenesis, the active formation of new blood vessels from pre-existing ones, is a complex and demanding biological process that plays an important role in physiological as well as pathological settings. Recent evidence supports cell metabolism as a critical regulator of angiogenesis.
<>However, whether and how cell metabolism regulates endothelial growth factor receptor levels and nucleotide synthesis remains elusive. We here shown in both human cell lines and mouse models that during developmental and pathological angiogenesis, endothelial cells (ECs) use glutaminolysis-derived glutamate to produce aspartate (Asp) via aspartate aminotransferase (AST/GOT). Asp leads to mTORC1 activation which, in turn, regulates endothelial translation machinery for VEGFR2 and FGFR1 synthesis. Asp-dependent mTORC1 pathway activation also regulates de novo pyrimidine synthesis in angiogenic ECs.
<>These findings identify glutaminolysis-derived Asp as a regulator of mTORC1-dependent endothelial translation and pyrimidine synthesis. Our studies may help overcome anti-VEGF therapy resistance by targeting endothelial growth factor receptor translation.”[283.1]

Copper: Low POP

Copper is a prime mediator of Angiogenesis by way of VEGF.

“<>Copper promotion of angiogenesis has been known for more than two decades, but the mechanism of action of copper has not been explored until recently. Copper stimulation of factors involved in vessel formation and maturation, such as vascular endothelial growth factor (VEGF), is mainly responsible for its angiogenesis effect. Copper is required for the activation of hypoxia-inducible factor-1 (HIF-1), a major transcription factor regulating the expression of VEGF. Copper would be transported into nucleus by a copper chaperon for superoxide dismutase-1.
<>Copper is required for HIF-1 interaction with the hypoxia-responsive element of the target genes and ensures the formation of HIF-1 transcriptional complex, thus activating the expression of target genes including VEGF. On the other hand, excess copper can stabilize HIF-1alpha, the rate-limiting component of HIF-1, leading to its accumulation in cytoplasm and thus HIF-1 activation.
<>The essential role of copper in production of VEGF makes it implicated in anti-angiogenesis therapy, such as the application of copper chelators in cancer therapy. However, suppression of angiogenesis is involved in the progression of heart hypertrophy and its transition to heart failure, therefore copper supplementation improves hypertrophic heart disease conditions. This dilemma of copper implications in cancer therapy and heart hypertrophy dictates a comprehensive understanding of a patient's condition before an implementation of copper manipulation therapy for different diseases. In this context, a development of diagnosis for copper metabolic changes as well as a tissue-specific copper manipulation would greatly benefit patients with an implication of copper manipulation therapy.”[284]

Barley Beta-Glucans: Low POP

Barley is a great source of Beta-Glucans. Barley Beta-Glucans enhance angiogenesis through endothelial cell antioxidant protection, by decreasing superoxide (O2 (-)) and HIF1-a, which is paradoxical to the aforementioned research but sensical to include into this cycle due to its angiogenic effects, especially on an extended Pro-Inflammatory Cycle, to avoid pathological inflammation.

"<>Manganese superoxide dismutase (MnSOD), a foremost antioxidant enzyme, plays a key role in angiogenesis. Barley-derived (1.3) β-d-glucan (β-d-glucan) is a natural water-soluble polysaccharide with antioxidant properties. To explore the effects of β-d-glucan on MnSOD-related angiogenesis under oxidative stress, we tested epigenetic mechanisms underlying modulation of MnSOD level in human umbilical vein endothelial cells (HUVECs) and angiogenesis in vitro and in vivo. Long-term treatment of HUVECs with 3% w/v β-d-glucan significantly increased the level of MnSOD by 200% ± 2% compared to control and by 50% ± 4% compared to untreated H2 O2 -stressed cells. β-d-glucan-treated HUVECs displayed greater angiogenic ability.
<>In vivo, 24 hrs-treatment with 3% w/v β-d-glucan rescued vasculogenesis in Tg (kdrl: EGFP) s843Tg zebrafish embryos exposed to oxidative microenvironment. HUVECs overexpressing MnSOD demonstrated an increased activity of endothelial nitric oxide synthase (eNOS), reduced load of superoxide anion (O2 (-)) and an increased survival under oxidative stress.
<>In addition, β-d-glucan prevented the rise of hypoxia inducible factor (HIF)1-α under oxidative stress. The level of histone H4 acetylation was significantly increased by β-d-glucan. Increasing histone acetylation by sodium butyrate, an inhibitor of class I histone deacetylases (HDACs I), did not activate MnSOD-related angiogenesis and did not impair β-d-glucan effects. In conclusion, 3% w/v β-d-glucan activates endothelial expression of MnSOD independent of histone acetylation level, thereby leading to adequate removal of O2 (-) , cell survival and angiogenic response to oxidative stress. The identification of dietary β-d-glucan as activator of MnSOD-related angiogenesis might lead to the development of nutritional approaches for the prevention of ischemic remodeling and heart failure."[284.1]

Thiamine: Low POP

Thiamine, being the most vital essential nutrient for brain health, aside from Linoleic acid, is positively associated with angiogenesis, therefore it would be wise to supplement it during extended Pro-Cycles, and it may be the only *pro-angiogenic* method to mitigate Nicotine-induced neurodegeneration, except for DHEA.

"<>Our objective was to determine the relationships between levels of different dietary nutrients intake with circulating endothelial progenitor cells (EPC) and vascular endothelial function in type II diabetic patients. We studied the daily dietary nutrients intake, the numbers of circulating CD34(+)/KDR(+) EPC and CD133(+)/KDR(+) EPC

and brachial artery flow-mediated dilation (FMD) in 88 diabetic patients without prior cardiovascular diseases and 91 sex- and age-matched controls. Compared with controls, diabetic patients had lower CD133(+)/KDR(+) EPC count (48.3 +/- 5.2 vs. 84.6 +/- 7.6/microL, p < 0.001), CD34(+)/KDR(+) EPC count (311 +/- 41 vs. 412 +/- 36/microL, p = 0.045), and FMD (2.54 +/- 0.37% vs. 5.46 +/- 0.47%, p < 0.001).
<>After adjusted for age, sex, smoking history, body weight, hemoglobin A1c level, total calorie intake, other dietary vitamin intake, use of antihypertensives, and lipid lowering agents, a higher intake of thiamine was significantly associated with a higher level of circulating CD34(+)/KDR(+) EPC (beta = 0.49, p = 0.028) and CD133(+)/KDR(+) EPC (beta = 0.45, p = 0.037) in diabetic patients, but not in controls. Furthermore, an increased intake of thiamine from 1st to 4th quartile in diabetic patients independently predicted an absolute increase in FMD by 1.29% (p = 0.026, relative increase = 63.5%).
<>This study demonstrated that daily thiamine intake was positively correlated with the circulating number of EPCs and FMD in patients with type II diabetes, independent of other dietary nutrients intake."[284.2]

Low Dose Alcohol: Moderate POP

For the research on the angiogenic effect of Alcohol See: Common Recreational Chemicals: Alcohol.
Options of consumption:

A. 0.125g / kg: Consume the EtOH Pre-Workout (Exercise periods lasting one hour or less).
B. 0.25g / kg: Consume the EtOH Intra-Workout. (Exercise periods lasting two hours or more).

It is my *opinion* that these dosages of alcohol, if used as suggested, will result in a Blood Alcohol Content that is too low to cause immunodepression (resulting in muscle fibrosis, or tendon injury) and NR2B Receptor-induced excitotoxicity, e.g., a BAC that never exceeds 0.03%.

Remember these are dosages in grams, not percentages! Convert your alcohol beverage percentage and volume to grams of pure alcohol with an online Alcohol to grams calculator, and then calculate your maximal dosage of Low Dose Alcohol by your bodyweight in kilograms, and if possible, use a Blood Alcohol Calculator to ensure you never exceed a BAC of 0.03%.

If you have a brain unaccustomed to EtOH, then it is probable that the RACK1-mediated Dorsomedial Striatum Neurogenic response (DSN) to EtOH is still intact, thus if you are looking to use EtOH as a nootropic above all else, use it in 24h cycles i.e., one day on, one day off, to allow RACK1 to reset its position (nuclear compartmentalization). [See: Recreational Chemicals: Alcohol]
The greatest benefit from Alcohol you will experience will be from consuming it before or during cardiovascular exercise (all intensities), as you will form new blood vessels in the brain and heart, thus increasing your intelligence and lifespan.

Regarding chronic consumption (all day), although I do not think that the DSN response will be permanently desensitized if you take 48h off every week from a protocol of all day low dose alcohol consumption, bDNF may become dysregulated but I am not certain as the research on low dose alcohol and chronic administration is limited, albeit people commonly already consume low doses of alcohol by sipping a large bottle of Kombucha every day, all day, especially and quite ironically previous alcoholics, where it seems to benefit them. Do understand that some 12-16oz bottles of Kombucha contain more alcohol than one N/A Beer.[284.2.1]
Regarding my favorite sources of Low Dose Alcohol, aside from GT Dave's Kombucha, there is O'Douls Beer (0.5%), Corona N/A, and there is Miller Extra Light Beer (2.8%). Interestingly, there are also Non-Alcoholic (0.5% - EtOH) wines available in certain big box stores, which is good news for housewives. Unfortunately, I must mention that it is not wise to use liquors, even if dosed properly, on Low Dose Alcohol protocols, as their consumption will assuredly result in an uncontrollably rapid rise in BAC, whereas Beer generally results in a slower and lessened peak BAC due to the protein, carbohydrates, and extra H2O present within each bottle, similarly I assume to N/A wine, making Beer firstly, and wine secondly, the best sources of Low Dose Alcohol.

High-Dose Alcohol: N/A POP

If getting drunk (binge drinking) is something you are intent on continuing, one day per week or one day per month, etc., then you can still utilize alcohol to promote angiogenesis, as it is both angiogenic during use and during withdrawal from its use, including stimulating a systemic inflammatory response, although this is not suggested as you will eventually suffer both muscle fibrosis, muscle atrophy, and tendon damage.

[A] Chronic Alcohol withdrawal promotes systemic angiogenesis through promoting VEGF-A Receptor activity.

"<>Vascular endothelial growth factor A (VEGF-A) is a key regulator of angiogenesis. This study investigated VEGF-A serum levels during alcohol withdrawal (days 1, 7 and 14, 76 male patients, 38 healthy controls). Patients showed significantly higher VEGF-A serum levels ($t = 2.620$, $P = 0.010$), which increased significantly during withdrawal ($F = 4.484$, $P = 0.014$, mean difference = -36.835, $P = 0.037$). The increase of VEGF-A serum levels was significantly associated with initial breath alcohol concentration and the sumscore of the severity scale of alcohol dependence (SESA questionnaire, $F = 5.252$, $P = 0.008$). Increase of VEGF-A serum levels is closely associated to alcohol intoxication and severity of alcohol dependence."[284.3A]

[B] Chronic Alcohol withdrawal promotes systemic IL-6 / TNF-a production, making it an excellent idea to plan an extremely damaging workout for the day after drinking excessively.

"<>We investigated the serum levels of IL-6 and TNF-α in 30 male alcohol-dependent patients during withdrawal (day 1, 7, and 14) and compared them with the levels obtained from 18 healthy male controls. IL-6 (day 1: T = 2,593, p = 0.013; day 7: T = 2,315, p = 0.037; day 14: T = 1,650, p = 0.112) serum levels were significantly increased at the beginning of alcohol withdrawal.
<>TNF-α (T = 3,202, p = 0.03) serum levels were significantly elevated in the patients' group during the whole period of withdrawal. IL-6 serum levels decreased significantly during withdrawal (F = 16.507, p < 0.001), whereas TNF-α levels did not change significantly (day 1-14). IL-6 serum levels were directly associated with alcohol consumption (r = 0.392, p = 0.047) on day 1. Moreover, the IL-6 serum levels were associated with alcohol craving (PACS total score day 1: r = -0.417, p = 0.022, the score of the obsessive subscale of the OCDS on day 14 [r = -0.549, p = 0.022]), depression (r = -0.507, p = 0.005), and trait anxiety (r = -0.674, p < 0.001) on day 1.
<>Our results support an association between alterations in TNF-α and IL-6 serum levels and alcohol consumption."[284.3B]

L-Ornithine: Low POP

L-Ornithine through polyamine breakdown products enhances angiogenesis, but more impressively, the breakdown product of Ornithine, Spermidine, associates with lifespan. [See: Fasting]

"<>Influences of L-arginine and L-ornithine supplementation on capillary growth. While L-arginine is metabolized to NO, it is catalyzed by arginase to produce L-ornithine. L-Ornithine is converted to putrescine by ornithine decarboxylase (ODC), after which putrescine is converted to spermidine and spermine. These polyamines are known to be required for mammalian cell growth and life. Overexpression of ODC enhanced endothelial cell proliferation possibly by suppressing endostatin, a carboxy-terminal fragment of type XVIII collagen, which inhibits endothelial pro-liferation, angiogenesis, and tumour growth."[284.4]

[Potassium Chloride, showing little to no inhibitory effect angiogenesis is permitted and encouraged to be used on this cycle, although its excessive use may negatively impact your bodies magnesium and sodium balance leading to paradoxical muscle cramping]

Angio-Teno Peptides
(Only for experimentation under the guidance of licensed medical doctor)

Two *research* peptides are of interest for the Pro-Cycle, **BPC-157** [A] and **Thymosin Beta-4** [B], both of which appear to accelerate wound healing. Although research is limited on their effects on myoblasts, and muscle tissue, I am reasonably certain that they promote angiogenesis and promote tendon collagen synthesis (hence the term I have invented "*Angio-Teno*", they are therefore suggested for use post-exercise, through intramuscular or peritendinous site injection, in four to six different spots (new

areas every week), to hypothetically magnify intramuscular angiogenesis, and / or tendon regeneration.

It must be noted that these peptides may very well perturb myogenic proliferation, cause muscle fibrosis, or even atrophy myotubes, they are therefore only suggested for use infrequently, and only after low-moderate load angiogenic exercise, or as a last resort for experimental injury treatment.

Because the majority of peptides are synthesized in, and sourced from China, they are liable to contain endotoxins, if you therefore experience an inflammatory reaction in or near to an injection site, your product is likely tainted.

Finally, if you find yourself living with a severe tendon injury and are desperate for an emergency alternative treatment option beyond surgery, you should invest your money in HPLC peptide analysis to confirm the peptide products you are purchasing or using currently are valid, and not merely toxic junk, as the cumulative cost of research peptides is no a laughing matter for the average gymgoer.

[A] BPC 157 promotes angiogenesis by way of VEGF receptor 2.

"<>BPC 157, a pentadecapeptide with extensive healing effects, has recently been suggested to contribute to angiogenesis. However, the underlying mechanism is not yet clear. The present study aimed to explore the potential therapeutic effect and pro-angiogenic mechanism of BPC 157.
<>As demonstrated by the chick chorioallantoic membrane (CAM) assay and endothelial tube formation assay, BPC 157 could increase the vessel density both in vivo and in vitro, respectively. BPC 157 could also accelerate the recovery of blood flow in the ischemic muscle of the rat hind limb as detected by laser Doppler scanning, indicating the promotion of angiogenesis.
<>Histological analysis of the hind limb muscle confirmed the increased number of vessels and the enhanced vascular expression of vascular endothelial growth factor receptor 2 (VEGFR2) in rat with BPC 157 treatment. In vitro study using human vascular endothelial cells further confirmed the increased mRNA and protein expressions of VEGFR2 but not VEGF-A by BPC 157. In addition, BPC 157 could promote VEGFR2 internalization in vascular endothelial cells which was blocked in the presence of dynasore, an inhibitor of endocytosis. BPC 157 time dependently activated the VEGFR2-Akt-eNOS signaling pathway which could also be suppressed by dynasore. The increase of endothelial tube formation induced by BPC 157 was also inhibited by dynasore.
<>This study demonstrates the pro-angiogenic effects of BPC 157 that is associated with the increased expression, internalization of VEGFR2, and the activation of VEGFR2-Akt-eNOS signaling pathway. BPC 157 promotes angiogenesis in CAM assay and tube formation assay. BPC 157 accelerates the blood flow recovery and vessel number in rats with hind limb ischemia. BPC 157 up-regulates VEGFR2 expression in rats with hind limb ischemia and endothelial cell culture. BPC 157 promotes VEGFR2 internalization in association with VEGFR2-Akt-eNOS activation."[284.5]

[B] Thymosin Beta 4 promotes angiogenesis by way of NF-kB pathway.

“<>Thymosin-β 4 (Tβ4) has been reported to exert a pro-angogenic effect on endothelial cells. However, little is known on the role and underlying mechanisms of Tβ4 on critical limb ischemia (CLI).
<>The present study aimed therefore to investigate the mechanisms and pro-angiogenic effects of Tβ4 in CLI mice. Tβ4 overexpression lentiviral vector was first transfected into HUVEC and CLI mice model, and inhibitors of Notch pathway (DAPT) and NF-κB pathway (BMS) were also applied to HUVEC and CLI mice. Subsequently, MTT, tube formation and wound healing assays were used to determine the cell viability, angiogenesis and migratory ablity of HUVEC, respectively. Western blotting, reverse transcription, quantitative PCR, immunofluorescence and immunohistochemistry were used to detect the expression of the angiogenesis-related factors angiopoietin-2 (Ang2), TEK receptor tyrosine kinase 2 (tie2), vascular endothelial growth factor A (VEGFA), CD31 and α-smooth muscle actin (α-SMA) and the Notch/NF-κB pathways-related factors NOTCH1 intracellular domain (N1ICD), Notch receptor 3 (Notch3), NF-κB and p65 in HUVEC or CLI mice muscle tissues.
<>The results demonstrated that Tβ4 not only enhanced the cell viability, angiogenesis and migratory ability of HUVEC but also promoted the expression of Ang2, tie2, VEGFA, N1ICD, Notch3, NF-κB, and phosphorylated (p)-p65 in HUVEC. In addition, Tβ4 promoted the expression of CD31, α-SMA Ang2, tie2, VEGFA, N1ICD and p-p65 in CLI mice muscle tissues. Treatment with DAPT and BMS had opposite effects of Tβ4, whereas Tβ4 reversed the effect of DAPT and BMS.
<>The findings from the present study suggested that Tβ4 may promote angiogenesis in CLI mice via regulation of Notch/NF-κB pathways.”[284.6]

Pro-Inflammation (Angiogenic) Cycle Dietary Fats

Linoleic Acid

An often-vilified fatty acid that is associated with mood and muscle growth. I would suggest a vegetable oil not high in vitamin e, and one not associated with anti-angiogenic research such as Sunflower Seed oil, or for a better and more neutral taste, Grapeseed oil.

[A] Linoleic acid enhances hypertrophy.

"<>Cell fusion of embryonic chick myoblasts has been studied in the presence of fat-soluble agents that induce erythrocytes to fuse. Retinol inhibited myoblast fusion but the cells recovered their ability to fuse within 48 h of removal of the retinol from the medium. Myristic acid, oleic acid, glycerol monooleate, linolenic acid and arachidonic acid similarly prevented fusion in myogenic cultures. By contrast, linoleic acid moderately enhanced the fusion of chick skeletal myoblasts. In addition, stearic acid, which does not fuse erythrocytes, inhibited myoblast fusion whereas the saturated, non-fusogenic fatty acid, arachidic acid, was without effect.”[289]

[B] Linoleic acid is angiogenic.

"<>LA reduced the wound area 14 days after wound induction. LA also increased the concentrations of cytokine-induced neutrophil chemotaxis (CINC-2αβ), tumor necrosis factor-α (TNF-α) and leukotriene B4 (LTB4), and reduced the expression of macrophage chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 (MIP-1). These results together with the histological analysis, which showed accumulation of leukocytes in the wound early in the healing process, indicate that LA brought forward the inflammatory phase and improved wound healing in diabetic rats. Angiogenesis was induced by LA through elevation in tissue content of key mediators of this process: vascular-endothelial growth factor (VEGF) and angiopoietin-2 (ANGPT-2)."[290]

[C] Repeated for Effect: Linoleic acid serum concentration is inversely associated with depression, and mental illness.

"<>By analogy with the above example, we propose that linoleic acid's concentration in the membrane of neurons or glia acts as a control parameter (corresponding to temperature for magnetic systems), effectively behaving like a switch in a system close to criticality, i.e., resulting in a phase transition between a normal brain and a pathological brain when the linoleic acid concentration falls below its set value."
"<>Recent observations, conducted on the characterization of the platelet fatty acids in mood disorders and ischemic heart disease have consistently shown that a very low concentration of linoleic acid is correlated with these diseases. This observation was found to be particularly interesting in brains of depressed subjects who had completed suicide."[291]

Sunflower Seed oil

To my present knowledge, Sunflower Seed oil is the only vegetable oil I have found that has shown no anti-angiogenic potential on PubMed, but instead pro-angiogenic and pro-inflammation potential. Making it an essential source of LA / OLE on the Pro-Cycle. It is important to purchase organic or solvent-free Sunflower Seed oil to avoid any to unwanted health effects from its consumption.

"<>In general, HFD induced and increase in the pro-inflammatory cytokine IL6 and decrease in the anti-inflammatory cytokine IL10 contents in the insulin target tissues (liver, skeletal muscle, and adipose tissue). Interestingly, sunflower oil supplementation itself (CD + n-6 group) for 12 weeks increased the content of the proinflammatory cytokine IL6 in all tissues. However, when the sunflower oil was associated with HFD (HFD + n-6 group), cytokine concentrations were similar to that found in the HFD group, in liver and adipose tissue."[291.2]

Lauric Acid (Coconut oil)

Lauric Acid is inflammatory, but Capric and Caprylic Acid are not, therefore you must avoid MCT oil during this cycle. If Coconut oil is moderately consumed, I do not believe the anti-inflammatory, or to be precise, potential anti-angiogenic effects, of Capric / Caprylic Acid, will present themselves biologically speaking.

[A] Lauric Acid appears to be angiogenic & inflammatory through COX2 expression, although research is limited.

"<>Lauric acid can decrease the time for complete epithelialization, because lauric acid can increase proliferation cells and migration cells."[292]

[B] Lauric Acid through TLR4 enhances fast twitch fiber growth. This is quite strange considering I believe MCT's promote slow twitch fiber growth, but it goes to show how versatile Coconut oil is for promoting myogenesis in all its forms.

"<>Lauric acid (LA), which is the primary fatty acid in coconut oil, was reported to have many metabolic benefits. TLR4 is a common receptor of lipopolysaccharides and is involved mainly in inflammation responses. Here, we focused on the effects of LA on skeletal muscle fiber types and metabolism.
<>We found that 200 μM LA treatment in C2C12 or dietary supplementation of 1% LA increased MHCIIb protein expression and the proportion of type IIb muscle fibers from 0.452 ± 0.0165 to 0.572 ± 0.0153, increasing the mRNA expression of genes involved in glycolysis, such as HK2 and LDH2 (from 1.00 ± 0.110 to 1.35 ± 0.0843 and from 1.00 ± 0.123 to 1.71 ± 0.302 in vivo, respectively), decreasing the catalytic activity of lactate dehydrogenase (LDH), and transforming lactic acid to pyruvic acid. Furthermore, LA activated TLR4 signaling, and TLR4 knockdown reversed the effect of LA on muscle fiber type and glycolysis. Thus, we inferred that LA promoted glycolytic fiber formation through TLR4 signaling."[293]

[C] Lauric Acid promotes neuronal IL-6 and ERK expression in the brain to promote neurite outgrowth, and synaptic maturation.

"<>Previous studies have suggested the potential efficacy of middle chain fatty acids (MCFAs) in the treatment of mood disorders and cognitive dysfunction. MCFAs are metabolized to ketone bodies in astrocytes; however, their effects on neuronal development including neurotrophic factor level are not well-understood. In the present study, we examined the effect of MCFAs on the mRNA expression of growth factors and cytokines in primary cultures of cortical astrocytes. The effect of MCFAs on neuron-astrocyte interaction in neuronal maturation was also determined using co-culture and astrocyte-conditioned medium.
<>Lauric acid (LA) typically increased the mRNA expression of glial-derived neurotrophic factor (Gdnf), interleukin-6 (Il6), and C–C motif chemokine 2 (Ccl2) in astrocytes. LA-induced phosphorylation of extracellular signal-regulated kinase contributed to these changes. In primary cultures of cortical neurons containing

astrocytes, LA enhanced the presynaptic protein levels. Astrocyte-conditioned medium after LA treatment also enhanced the presynaptic protein levels in the cortical neuron cultures. These results suggest that LA increase the mRNA expression of GDNF and cytokines in astrocytes, and thereby, enhances the presynaptic maturation."[293.1]

Oleic Acid

Although Oleic acid is slightly anti-inflammatory via suppressing IL-6 & promotes muscle lipid accumulation [See: Muscle Lipid Accumulation], it does enhance angiogenesis, and is found in most vegetable oils, making it an unintended and potentially beneficial addition to this cycle and nearly every diet on earth. If you are obese you must absolutely avoid consuming excess Oleic acid, as you will only cause further derangement to your metabolism, and further delay reaching your lipolytic goals. I do understand that when large amounts of Oleic acid are acutely administered, a general anti-inflammatory physiological effect will result, but over time, as intramuscular lipid accumulation progresses, so too will insulin resistance, leading to a chronic and unbeneficial levels of inflammation.

"<>The current study determined the natural angiogenic molecules using an unbiased metabolomics approach. A chick chorioallantoic membrane (CAM) model was used to examine pro- and antiangiogenic molecules, followed by gas chromatography-mass spectrometry (GCMS) analysis. Vessel formation was analyzed quantitatively using the angiogenic index ($p < 0.05$). At embryonic day one, a white streak or circle area was observed when vessel formation begins. GCMS analysis and database search demonstrated that angiogenesis may initiate when oleic, cholesterol, and linoleic acids increased in the area of angiogenic reactions. The gain of function study was conducted by the injection of cholesterol and oleic acid into a chick embryo to determine the role of each lipid in angiogenesis.
<>We propose that oleic acid, cholesterol, and linoleic acid are natural molecules that set the platform for the initiation stage of angiogenesis before other proteins including the vascular endothelial growth factor, angiopoietin, angiotensin, and erythropoietin join as the angiome in sprout extension and vessel maturation."[294]

Pro-Inflammation (Angiogenic) Cycle Diet

On the Pro-Cycle it is vital that you avoid consuming foods high in antioxidants, including vitamins, phytochemicals, & minerals. I suggest eating only pearled barley, barley flour pasta, barley flour bread, and Nattō made with your choice of beans (excluding soybeans) each meal as your carbohydrate source if you are not on the Ketogenic Diet, adding 1-Tbsp of Sunflower oil (Linoleic / Oleic acid) & 1-Tbsp of Coconut oil (Lauric Acid) to each meal.

Do not consume supplemented Glycine during an angiogenic Pro-Cycle as it exhibits anti-angiogenic potential in high concentrations, whereas Serine, although being a precursor to Glycine, may enhance angiogenesis.

If you are using large amounts of Nicotine on a Pro-Cycle, it is unwise to consume large amounts of macronutrients, especially carbohydrates and fatty acids, as you will be exposing your cells to an excessive amounts of ROS. It is a better idea to eat very small meals and engage in antiquated caloric restriction (restricting all macronutrients each meal, primarily carbs and fat). Another option for Nicotine use is to use it while fasting, which is a far better idea if you are prone to overeating.

Of note, Protein Restriction, or to be precise, ***Methionine & Cysteine dietary restriction*** promotes angiogenesis in skeletal muscle through increased hydrogen sulfide production from Endothelial Cells. It therefore may be intelligent to restrict protein intake on low-moderate intensity exercise days to further magnify angiogenic processes, or an even better idea is to combine angiogenic workouts such as Aerobics, Cardio, and Occlusion training with fasting:

"<>Dietary restriction (DR), defined as reduced nutrient/energy intake without malnutrition, is best known for its ability to extend lifespan, improve metabolic fitness, and increase stress resistance. DR regimens, which vary widely, can emphasize either restriction of total food intake (calorie restriction, CR) or dilution of specific nutrients in the diet, such as the sulfur AAs (SAAs) methionine (M) and cysteine (C) (M restriction, MR).
<>We recently reported that CR increases hepatic CGL expression, endogenous H2S production capacity, and resistance to hepatic ischemia reperfusion injury, each of which is abrogated by dietary C supplementation. CR also promotes revascularization and recovery from femoral artery ligation in rodents and maintains vascular health in rodents and non-human primates in part by preserving capillary density in skeletal muscle."[294.A]

Fasting (specifically fasted exercise) may also prove to be a valuable method to promote systemic angiogenesis.

"<>Obesity and insulin resistance are associated with low-grade systemic inflammation, which is related to increased concentrations of plasma FFAs, glucose, or insulin.
<>Prolonged fasting induces insulin resistance due to elevated plasma FFAs, but is not accompanied by hyperinsulinemia or hyperglycemia. This makes it possible to study effects of physiologically increased FFA concentrations on inflammatory markers, when insulin and glucose concentrations are not increased.
<>In random order, 10 healthy young lean men (mean BMI: 22.8 kg/m2) were fasted or fed in energy balance for 60 h with a 2-week wash-out period. Subjects stayed in a respiration chamber during the 60-h periods. Blood samples were taken after 12, 36, and 60 h. Then, a hyperinsulinemic-euglycemic clamp was performed. Fasting decreased insulin sensitivity by 45% and increased FFA concentrations 5-fold. Fasting did not

change concentrations of the inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-8, or of hs-CRP. Effects on vascular endothelial growth factor (VEGF)--which may positively relate to insulin resistance, and on chemerin and leptin--adipokines related to obesity, and obesity-related pathologies, were also studied.
<>At t=60 h, VEGF concentrations were significantly increased during the fasted period ($p<0.05$). At the same time point, chemerin ($p<0.01$) and leptin ($p<0.01$) were significantly decreased after fasting. For leptin, this decrease was also significant after 36 h ($p<0.01$). Adiponectin levels remained unchanged.
<>In healthy young lean men, fasting-induced increases in FFAs leading to insulin resistance do not cause changes in concentrations of the inflammatory cytokines. VEGF concentrations increased and those of chemerin decreased."[294.B]

[See: Fasting] [See: IMC Workout Protocols: Angio-Fast Protocol]

Sodium intake must be kept at a bare minimum to avoid inhibiting angiogenesis, Do not use Potassium without Sodium or an imbalance may occur. Conversely, on an Anti-Cycle, salt loading is permitted to facilitate muscle performance, and to replenish the sodium that will be lost from high frequency Hyperthermia Therapy.

"<>High sodium intake is associated with the development of cardiac hypertrophy in man and rats independently of the rise of blood pressure. In addition, the reduced capillary density observed in striated muscle of rats fed a high salt diet suggests that angiogenesis is altered. The aim of the present experiments was to investigate the angiogenic capacities of vascular rings isolated from the aorta and the coronary artery of rats. Vascular rings (external diameter of 1 669 +/- 9 and 323 +/- 26 microm for aorta and coronary artery. respectively) are cultured in a three-dimensional collagen type I lattice and a standard medium (DMEM+HAMF12) containing 152 mM of sodium. Sodium ion associated with chloride or citrate is added to the standard medium to achieve a final concentration of sodium of 160 and 176 mM. The role of sodium-proton exchanger is evaluated through the addition of amiloride to the culture medium. Sprouts formed from vascular explants are counted every second day until days 8 to 10. Kinetics of new vessels formation and the number of sprouts were similar in aortic and coronary rings (83 +/- 5 and 95 +/- 5 sprouts, respectively). <>Elevation of sodium chloride concentration inhibits by 50 to 80% the neo-vessels formation in both the aorta and the coronary artery. Anti-angiogenic effect of the high sodium medium was not affected when citrate was substituted to chloride. Amiloride (3.10(-5) M) reduced the number of sprouts formed in the standard medium; however, it counteracted the anti-angiogenic effect of elevated sodium concentration.
<>These results indicate that high extracellular concentration of sodium and not chloride anion is accompanied by a deleterious effect on angiogenic capacities of cultured aortic and coronary artery rings through modifications of trans-membrane sodium exchanges."[294.0]

Pro-Inflammation (Angiogenic) Cycle Modalities

Hyperthermia Therapy (Sauna)

[Remember Hyperthermia results in an inflammatory response of ROS generation, do not utilize in this therapy every single day unless you engage in frequent cardiovascular training to protect your brain cells]

Heat stress substantially increases skeletal muscle IL-6 release and TNF-a production, making this therapy absolutely essential for athletes.

"<>Skeletal muscles produce and contribute to circulating levels of IL-6 during exercise. However, when core temperature is reduced, the response is attenuated. Therefore, we hypothesized that hyperthermia may be an important and independent stimulus for muscle IL-6. In cultured C2C12 myotubes, hyperthermia (42°C) increased IL-6 gene expression 14-fold after 1 h and 35-fold after 5 h of 37°C recovery; whereas exposure to 41°C resulted in a 2.6-fold elevation at 1 h. IL-6 protein was secreted and significantly elevated in the cell supernatant. Similar but reduced responses to heat were seen in C2C12 myoblasts. Isolated soleus muscles from mice, exposed ex vivo to 41°C for 1 h, yielded similar IL-6 gene responses (>3-fold) but without a significant effect on protein release. When whole animals were exposed to passive hyperthermia, such that core temperature increased to 42.4°C, IL-6 mRNA in soleus increased 5.4-fold compared with time matched controls. <>Interestingly, TNF-α gene expression was routinely suppressed at all levels of hyperthermia (40.5-42°C) in the isolated models, but TNF-α was elevated (4.2-fold) in the soleus taken from intact mice exposed, in vivo, to hyperthermia. Muscle HSP72 mRNA increased as a function of the level of hyperthermia, and IL-6 mRNA responses increased proportionally with HSP72. In cultured C2C12 myotubes, when heat shock factor was pharmacologically blocked with KNK437, both HSP72 and IL-6 mRNA elevations, induced by heat, were suppressed. These findings implicate skeletal muscle as a "heat stress sensor" at physiologically relevant hyperthermia, responding with a programmed cytokine expression pattern characterized by elevated IL-6."[294.1]

Deep-Tissue Massage

Concerning deep-tissue massage, the greater the pain, the greater the blood vessel shear stress and angiogenesis.

[A] Deep-Tissue Massage is angiogenic, although this effect subsides after around four weeks if the massages are administered daily.

"<>Rats Given Massages every day post-workout have greater VEGF-A content in their muscles, compared to rats given a massage pre-workout only. "Our results demonstrate the most pronounced increases in the expression of VEGF-A, CD34, and FGF-2 genes and of VEGF-A protein, in the group of rats subjected to massage (group M)."[295]

[B] Deep-Tissue Massage increases myogenic proliferation & costamerogenesis if utilized *immediately* post-workout, albeit it slightly suppresses IL-6 / NF-kB.

"<>We found that massage activated the mechanotransduction signaling pathways focal adhesion kinase (FAK) and extracellular signal–regulated kinase 1/2 (ERK1/2), potentiated mitochondrial biogenesis signaling [nuclear peroxisome proliferator–activated receptor γ coactivator 1α (PGC-1α)], and mitigated the rise in nuclear factor κB (NFκB) (p65) nuclear accumulation caused by exercise-induced muscle trauma. Moreover, despite having no effect on muscle metabolites (glycogen, lactate), massage attenuated the production of the inflammatory cytokines tumor necrosis factor–α (TNF-α) and interleukin-6 (IL-6) and reduced heat shock protein 27 (HSP27) phosphorylation, thereby mitigating cellular stress resulting from myofiber injury."[296]

Blood Flow Restriction Training

Kaatsu Training, B.F.R. Training, or Occlusion Training is a new technique to enhance myogenesis through increased stem cell release, and magnified angiogenesis post-training. It has its risks as you will soon learn, but in my experience, aside from long aerobic warmups and lactic acid training it is the only feasible way a natural athlete can maximize their myogenic potential.

The percentage of occlusion should always be at or above 60%, which is something sadly unknowable to anyone without an expensive set of BFR cuffs. Although I can confidently suggest that if you experience extreme limb pain and failure after around 30-120 seconds of an occluded exercise "set", your occlusion percentage is sufficient to stimulate muscle growth.

The lower the 1RM percentage you lift (< 30%), the greater occlusion percentage you will need to exert a noticeable myogenic effect. Conversely, the greater load you lift (40%+) the less effect blood flow restriction training will have on myogenesis, clearly because with higher loads comes lower repetitions, and with lower repetitions comes less exercise-induced hypoxia. Although exposing a muscle to hypoxia will likely stimulate angiogenesis regardless of exercise, it is only through exercise in a hypoxic cellular environment that true adaptation occurs.

Repetitions per set should never fall below thirty, ideally exceeding sixty, & they should always be regular-speed or a faster tempo, as it is the hypoxia that occurs in muscle tissue during high volume work that leads to the compensatory processes that promote angiogenesis.

As for isolation or compound exercises to perform during Occlusion Training, I would suggest a majority of sets be compound movements, as this will increase Hematopoietic Stem Cell production moreso than isolation movements, in my hypothesis, and this would result in greater muscle growth to the muscles adjacent to the occluded ones.
Hypoxia tends to stimulate excessive autophagy, which means Occlusion Training may harm skeletal muscle cells, depending on the degree and frequency of hypoxia, but only time and new research will reveal more details on this. I however believe strongly that

precisely like the benefits of intermittent ROS, intermittent hypoxia is likely to beneficial to the function of our muscle tissue and our brains.
Remember: Performing sets of twelve repetitions, or triples, or singles (high loads) with BFR cuffs will result in no benefits. Consider buying a marine tourniquet or a cheap Amazon.com tourniquet as an alternative to commercially available & overpriced B.F.R. cuffs.

[See: IMC Workout Protocols: Incremental Occlusion Training (IOT)]

[A] B.F.R. Training increases Myonuclei numbers in muscle, but strenuous occlusion training may slow recovery, or cause the adaptive process of myonuclear accretion to plateau, indicating this form of training should be cycled. Although I do not believe that the angiogenesis benefits of B.F.R. Training dissipate so quickly.

"<>The purpose of the present study was to investigate muscle hypertrophy, strength, and myonuclear and satellite cell (SC) responses to high-frequency blood flow-restricted resistance exercise (BFRRE). Thirteen individuals [24 ± 2 yr (mean ± SD), 9 men] completed two 5-day blocks of 7 BFRRE sessions, separated by a 10-day rest period. <>Four sets of unilateral knee extensions to voluntary failure at 20% of one repetition maximum (1RM) were conducted with partial blood flow restriction (90-100 mmHg). Muscle samples obtained before, during, 3 days, and 10 days after training were analyzed for muscle fiber area (MFA), myonuclei, SC, and mRNA and miRNA expression. Muscle size was measured by ultrasonography and magnetic resonance imaging and strength with 1RM knee extension.
<>With the first block of BFRRE, SC number increased in both fiber types (70%-80%, $P < 0.05$), whereas type I and II MFA decreased by 6 ± 7% and 15 ± 11% ($P < 0.05$), respectively. With the second block of training, muscle size increased by 6%-8%, whereas the number of SCs (type I: 80 ± 63%, type II: 147 ± 95%), myonuclei (type I: 30 ± 24%, type II: 31 ± 28%), and MFA (type I: 19 ± 19%, type II: 11 ± 19%) peaked 10 days after the second block of BFRRE, whereas strength peaked after 20 days of detraining (6 ± 6%, $P < 0.05$). Pax7- and p21 mRNA expression were elevated during the intervention, whereas myostatin, IGF1R, MyoD, myogenin, cyclinD1 and -D2 mRNA did not change until 3-10 days postintervention.
<>High-frequency low-load BFRRE induced robust increases in SC, myonuclei, and muscle size but modest strength gains. Intriguingly, the responses were delayed and peaked 10-20 days after the training intervention, indicating overreaching.
<>NEW & NOTEWORTHY In line with previous studies, we demonstrate that high-frequency low-load blood flow-restricted resistance exercise (HF-BFRRE) can elicit robust increases in satellite cell and myonuclei numbers, along with gains in muscle size and strength. However, our results also suggest that these processes can be delayed and that with very strenuous HF-BFRRE, there may even be transient muscle fiber atrophy, presumably because of accumulated stress responses. Our findings have implications for the prescription of BFR exercise."[297]

[B] Quite obviously, Occlusion Training enhances angiogenesis.

"<>BFR exercise enhanced mRNA expression of vascular endothelial growth factor (VEGF) at 2 h (5.2 ± 2.8 vs 1.7 ± 1.1; p = .02) and 4 h (6.8 ± 4.9 vs. 2.5 ± 2.7; p = .01) compared to CON. mRNA expression of VEGF-R2 and hypoxia-inducible factor 1α increased following BFR exercise but only eNOS were enhanced relative to CON. Matrix metalloproteinase-9 mRNA expression was not altered in response to either exercise. Acute low-load resistance exercise with BFR provides a targeted angiogenic response potentially mediated through enhanced ischaemic and shear stress stimuli."[298]

[C] B.F.R. Training increases the production of Hematopoietic Progenitor Cells, which then convert into either white blood cells or red blood cells, making this method of training systemically immunostimulatory, and quite possibly life extending.

"<>Purpose: To determine the effects of blood flow restriction (BFR) exercise on $CD34^+$ cells, platelets, white blood cells, neutrophils, lymphocytes, lactate, and glucose.
<>Methods: Healthy participants aged 20 to 39 years who were able to perform the exercise sessions were recruited. Participants underwent an experimental (EXP) occluded testing session and a control (CON) session using the Delfi Personalized Tourniquet System. Blood draws were performed prior to testing and immediately after the exercise session. Blood analysis consisted of a complete blood count as well as flow cytometry to measure peripheral $CD34^+$ counts as a marker for hematopoietic progenitor cells.
<>Results: Fourteen men (aged 30.8 ± 3.9 years) volunteered. There was a significant increase in average $CD34^+$ counts immediately after the EXP session only (3.1 ± 1.2 cells · μL^{-1} vs 5.2 ± 2.9 cells · μL^{-1}, $P = .012$). Platelet counts were significantly elevated after both sessions, with the average increase being higher after the EXP session (mean difference [MD], 34,200/μL; $P < .002$) than after the CON session (MD, 11,600/μL; $P < .002$). White blood cell counts significantly increased after both the EXP (8,400 ± 2,200/μL vs 6,300 ± 1,600/μL; $P < .001$) and CON (MD, 900/μL; $P < .001$) sessions. There was a significant increase from baseline to immediately after exercise in the average number of lymphocytes (MD, 6.3%; $P < .001$) and, conversely, a significant decrease in the average neutrophil count (MD, 6.5%; $P < .001$) in the EXP session only. Lactate levels significantly increased in the EXP (MD, 6.1 mmol · L^{-1}; $P = .001$) and CON (MD, 3.6 mmol · L^{-1}; $P = .001$) groups. No changes in glucose levels were observed.
<>Conclusions: Exercise with BFR causes a significant post-exercise increase in peripheral hematopoietic progenitor cells and platelets, beyond that of standard resistance training."[298.1]

[D] B.F.R. Training promotes mTOR to facilitate myogenesis.

"<>The loss of skeletal muscle mass during aging, sarcopenia, increases the risk for falls and dependence. Resistance exercise (RE) is an effective rehabilitation technique that can

improve muscle mass and strength; however, older individuals are resistant to the stimulation of muscle protein synthesis (MPS) with traditional high-intensity RE. Recently, a novel rehabilitation exercise method, low-intensity RE, combined with blood flow restriction (BFR), has been shown to stimulate mammalian target of rapamycin complex 1 (mTORC1) signaling and MPS in young men.
<>We hypothesized that low-intensity RE with BFR would be able to activate mTORC1 signaling and stimulate MPS in older men. We measured MPS and mTORC1-associated signaling proteins in seven older men (age 70+/-2 yr) before and after exercise. Subjects were studied identically on two occasions: during BFR exercise [bilateral leg extension exercise at 20% of 1-repetition maximum (1-RM) with pressure cuff placed proximally on both thighs and inflated at 200 mmHg] and during exercise without the pressure cuff (Ctrl). MPS and phosphorylation of signaling proteins were determined on successive muscle biopsies by stable isotopic techniques and immunoblotting, respectively. MPS increased 56% from baseline after BFR exercise ($P<0.05$), while no change was observed in the Ctrl group ($P>0.05$). Downstream of mTORC1, ribosomal S6 kinase 1 (S6K1) phosphorylation and ribosomal protein S6 (rpS6) phosphorylation increased only in the BFR group after exercise ($P<0.05$).
<>We conclude that low-intensity RE in combination with BFR enhances mTORC1 signaling and MPS in older men. BFR exercise is a novel intervention that may enhance muscle rehabilitation to counteract sarcopenia."[299]

[E] BFR Training with high loads yields little additional benefits, with only higher occlusion percentages + lower loads (1-30%) and higher volume work yielding effects. Low repetition exercise is not hypoxic enough.

"<>Purpose: We compared the effects of different protocols of blood-flow restriction training (BFRT) with different occlusion pressures and/or exercise intensities on muscle mass and strength. We also compared BFRT protocols with conventional high-intensity resistance training (RT).
<>Methods: Twenty-six subjects had each leg allocated to two of five protocols. BFRT protocols were performed at either 20 or 40 % 1-RM with either 40 or 80 % occlusion pressure: BFRT20/40, BFRT20/80, BFRT40/40, and BFRT40/80. Conventional RT was performed at 80 % 1-RM (RT80) without blood-flow restriction. Maximum dynamic strength (1-RM) and quadriceps cross-sectional area (CSA) were assessed at baseline and after 12 weeks.
<>Results: Regarding muscle mass, increasing occlusion pressure was effective only at very low intensity (BFRT20/40 0.78 % vs. BFRT20/80 3.22 %). No additional increase was observed at higher intensities (BFRT40/40 4.45 % vs. BFRT40/80 5.30 %), with no difference between the latter protocols and RT80 (5.90 %). Exercise intensity played a role in CSA when comparing groups with similar occlusion pressure. Muscle strength was similarly increased among BFRT groups (~12.10 %) but to a lesser extent than RT80 (21.60 %).
<>Conclusion: In conclusion, BFRT protocols benefit from higher occlusion pressure (80 %) when exercising at very low intensities. Conversely, occlusion pressure seems

secondary to exercise intensity in more intense (40 % 1-RM) BFRT protocols. Finally, when considering muscle strength, BFRT protocols seem less effective than high-intensity RT."[299.1]

[F] B.F.R. Training could exacerbate or cause cardiovascular events.

"<>Blood flow restriction (BFR) training (also known as Kaatsu training) is an increasingly common practice employed during resistance exercise by athletes attempting to enhance skeletal muscle mass and strength. During BFR training, blood flow to the exercising muscle is mechanically restricted by placing flexible pressurizing cuffs around the active limb proximal to the working muscle. This maneuver results in the accumulation of metabolites (e.g., protons and lactic acid) in the muscle interstitium that increase muscle force and promote muscle growth. <>Therefore, the premise of BFR training is to simulate and receive the benefits of high-intensity resistance exercise while merely performing low-intensity resistance exercise. This technique has also been purported to provide health benefits to the elderly, individuals recovering from joint injuries, and patients undergoing cardiac rehabilitation. Since the seminal work of Alam and Smirk in the 1930s, it has been well established that reductions in blood flow to exercising muscle engage the exercise pressor reflex (EPR), a reflex that significantly contributes to the autonomic cardiovascular response to exercise. However, the EPR and its likely contribution to the BFR-mediated cardiovascular response to exercise is glaringly missing from the scientific literature. Inasmuch as the EPR has been shown to generate exaggerated increases in sympathetic nerve activity in disease states such as hypertension (HTN), heart failure (HF), and peripheral artery disease (PAD), concerns are raised that BFR training can be used safely for the rehabilitation of patients with cardiovascular disease, as has been suggested.
<>Abnormal BFR-induced and EPR-mediated cardiovascular complications generated during exercise could precipitate adverse cardiovascular or cerebrovascular events (e.g., cardiac arrhythmia, myocardial infarction, stroke and sudden cardiac death). Moreover, although altered EPR function in HTN, HF, and PAD underlies our concern for the widespread implementation of BFR, use of this training mechanism may also have negative consequences in the absence of disease. That is, even normal, healthy individuals performing resistance training exercise with BFR are potentially at increased risk for deleterious cardiovascular events. This review provides a brief yet detailed overview of the mechanisms underlying the autonomic cardiovascular response to exercise with BFR. A more complete understanding of the consequences of BFR training is needed before this technique is passively explored by the layman athlete or prescribed by a health care professional."[300]

Low-Intensity Pulsed Ultrasound (LIPUS) Therapy

A new therapy science that offers promising angiogenic-promoting effects by activation of VEGF / bFGF through the use of soundwaves that penetrate through flesh.

"<>Along with the progress of global aging, the prognosis of severe ischemic heart disease (IHD) remains poor, and thus the development of effective angiogenic therapy remains an important clinical unmet need. We have developed low-energy extracorporeal cardiac shock wave therapy as an innovative minimally invasive angiogenic therapy and confirmed its efficacy in a porcine chronic myocardial ischemia model in animal experiments as well as in patients with refractory angina. Since ultrasound is more advantageous for clinical application than shock waves, we then aimed to develop ultrasound therapy for IHD. We demonstrated that specific conditions of low-intensity pulsed ultrasound (LIPUS) therapy improve myocardial ischemia in animal models through the enhancement of angiogenesis mediated by endothelial mechanotransduction. <>In general, some cases of refractory lymphedema cannot be completely cured even by surgery, and such patients have limited treatment options. Thus, we next examined the beneficial effects of low-energy SW therapy on animal models of secondary lymphedema in vivo. The results showed that SW therapy significantly enhanced the expressions of VEGF-C and basic fibroblast growth factor (bFGF), which improved the lymphatic system and lymphatic density. From these results, low-energy SW therapy may also induce therapeutic lymphangiogenesis in lymphedema through the upregulations of VEGF-C and bFGF, suggesting that SW therapy is a non-invasive therapy for patients with lymphedema."[300.1]

Local Vibration Therapy

The newest technology and one of the safest therapies to enhance muscle recovery, with the most promising effects being the acceleration of tendon healing. I suggest a 3500RPM-8,000RPM Random Orbital Car Polisher be used on your muscles & tendons, especially the injured ones, for a period of 40-minutes every day. From my experience anything below 3,500RPM isn't effective, nor is the therapy effective if the surface area circumference of the device head is below that of a standard 6-Inch Random Orbital *Car* Polisher as the sole purpose of its use is to enhance blood flow, making commonly sold exercise massage devices with tiny heads absolutely useless.
It must be mentioned that one should never apply great vibrations to their neck, as this may damage hearing cells, you should save the trapezius and neck muscle recovery therapy for deep tissue massage only.
Finally, I am aware that there are certain vibration technological products being sold now called Vibration Platforms which are gaining popularity in the fitness community, which may build leg bone density, but they are not to be considered equivalent or superior to locally applied extreme vibration therapy, such as from a Random Orbital Car Polisher. Furthermore, they may cause *spinal disc degeneration*, especially in the lumbar region (Note: Whole-body Vibration = Vibration Platform use):

"<>Objective: Whole-body vibration (WBV) is a popular fitness trend based on claims of increased muscle mass, weight loss and reduced joint pain. Following its original implementation as a treatment to increase bone mass in patients with osteoporosis, WBV

has been incorporated into clinical practice for musculoskeletal disorders, including back pain. However, our recent studies revealed damaging effects of WBV on joint health in a murine model. In this report, we examined potential mechanisms underlying disc degeneration following exposure of mice to WBV.
<>Methods: Ten-week-old male mice were exposed to WBV (45 Hz, 0.3 g peak acceleration, 30 min/day, 5 days/week) for 4 weeks, 8 weeks, or 4 weeks WBV followed by 4 weeks recovery. Micro-computed tomography (micro-CT), histological, and gene expression analyses were used to assess the effects of WBV on spinal tissues.
<>Results: Exposure of mice to 4 or 8 weeks of WBV did not alter total body composition or induce significant changes in vertebral bone density. On the other hand, WBV-induced intervertebral disc (IVD) degeneration, associated with decreased disc height and degenerative changes in the annulus fibrosus (AF) that did not recover within 4 weeks after cessation of WBV. Gene expression analysis showed that WBV for 8 weeks induced expression of Mmp3, Mmp13, and Adamts5 in IVD tissues, changes preceded by increased expression of Il-1β.
<>Conclusions: Progressive IVD degeneration induced by WBV was associated with increased expression of Il-1β within the IVD that preceded Mmp and Adamts gene induction. Moreover, WBV-induced IVD degeneration is not reversed following cessation of vibration."[300.2]

[A] Vibration Therapy enhances blood flow 1.

"<>Studies in healthy volunteers and patients with renal failure have shown that vibration, applied with a frequency of 47 Hz and a vibrational intensity of 600 mVpp, increases microcirculation of blood in the skin. This controlled, in vivo, experimental study was conducted to further evaluate the effect of vibration on skin microcirculation and to ascertain whether administration of a nitric oxide (NO) synthase inhibitor (NG-nitro-L-arginine methyl ester [L-NAME]) diminishes the effect of vibration on skin blood flow. Using a mouse microcirculatory model, 12 animals were prepared for study (six in the control and six in the experimental group). In the experimental group, vibrations were applied horizontally for 15 minutes. The control group received no vibration. Venular blood flow was measured using intravital videomicroscopy at baseline and at 0, 5, and 15 minutes after the application of vibration.
<>Vibration significantly increased the blood flow at 5 and 15 minutes after application (P = 0.002 and P = 0.046, respectively). Differences between the control and experimental group also were statistically significant (P = 0.0017 and P = 0.046, respectively). In the second study, all animals (seven in each group) received an intraperitoneal injection of NO synthase inhibitor L-NAME before vibration application. When NO synthase inhibitor L-NAME was administered, the increase in blood flow in the vibration group was minimal after 5 and 10 minutes, and nonexistent after 15 minutes."[301]

[B] Vibration Therapy enhances blood flow 2.

"<>1. The blood flow in rabbit gastrocnemius, as measured by photoelectric drop-counter, increased when the muscle was vibrated at frequencies of 22--62 Hz. 2. Blood flow increased rapidly within 1--2 s of the start of vibration, and lasted for the whole time vibration was applied. 3. The increase in blood flow was negatively correlated with the initial blood flow, being greater with lower flows. 4. The magnitude of increase was similar in both innervated and acutely denervated muscles. 5. The arterial blood pressure did not change apart from a very brief fall at the beginning of vibration. Venous pressure rose and, consequently, the perfusion pressure was lower. The increase in blood flow thus indicates a considerable dilatation in the resistance vessels of skeletal muscle."[302]

[C] Vibration Therapy promotes tendon healing.

“<>To investigate the role of low-magnitude, high-frequency vibration as a treatment to accelerate healing of an acute ligament injury and to examine gene expression in the intact Achilles tendon of the injured limb after low-magnitude, high-frequency vibration. <>Methods: Complete surgical transection of the medial collateral ligament (MCL) was performed in 32 Sprague-Dawley rats, divided into control and low-magnitude, high-frequency vibration groups. Low-magnitude, high-frequency vibration started on postoperative day 2, and rats received vibration for 30 minutes a day for 12 days. All rats were sacrificed 2 weeks after the operation, and their intact and injured MCLs were biomechanically tested or used for histological analysis. Intact Achilles tendons from the injured limb were evaluated for differences in gene expression.
>Results: Mechanical testing revealed no differences in the ultimate tensile load or the structural stiffness between the control and vibration groups for either the injured or intact MCL. Vibration exposure increased gene expression of collagen 1 alpha (3-fold), interleukin 6 (7-fold), cyclooxygenase 2 (5-fold), and bone morphogenetic protein 12 (4-fold) in the intact Achilles tendon when compared with control tendons ($P < .05$). <>Conclusion: While no differences were observed in the mechanical or histological properties of the fully transected MCL after low-magnitude, high-frequency vibration treatment, significant enhancements in gene expression were observed in the intact Achilles tendon. These included collagen, several inflammatory cytokines, and growth factors critical for tendons.”[303]

[D] Vibration Therapy stimulates hypertrophy through PAX7 and prevents disuse-induced Slow-Fast twitch muscle fiber conversion.

“<>Muscle atrophy can be caused by unloading stress such as microgravity environments or cast immobilization. Therapies for such disuse muscle atrophy and their underlying mechanisms are incompletely understood. Here, we investigated the therapeutic effects of local vibration stimulation on immobilization-induced skeletal muscle atrophy. A rat model was made by placing the left hindlimb in a cast for 1 week, leading to oxidative myofiber atrophy without myopathic changes in soleus skeletal muscle. Vibration

stimulus (90 Hz, 15 min) to the plantar fascia of the atrophic hindlimb was performed once a day using a hand-held vibration massager after removal of a cast at the end of the immobilization period.
<>After 2 weeks, rats were dissected, and quantitative analysis of the cross-sectional areas of soleus myofibers was performed. The results revealed that vibration induced significant recovery from disuse muscle atrophy, compared with untreated immobilized samples.
<>Furthermore, vibration treatment suppressed the fiber transition from slow to fast fiber types compared with vibration-untreated immobilized samples. Western blotting analyses of mechanical stress-induced factors revealed that the expression of mechano-growth factor (MGF), systemic insulin-like growth factor I, and the mechanotransduction protein, Yes-associated protein 1 (YAP1), was decreased in untreated immobilized soleus muscle, whereas vibration stimulation restored their expression. No change in the level of phosphorylation of YAP1Ser127 was observed, leading to no change in p-YAP1/YAP1 ratio in vibration-treated immobilized soleus muscle.
<>The results indicate that vibration stimulus is effective to restore immobilization-induced inactivation of YAP1 pathway. Phosphorylation of ERK 1/2, but not AKT, was enhanced in vibration-treated immobilized soleus muscle. Furthermore, vibration stimuli restored immobilization-induced downregulation of the paired box transcription factor, PAX7, a critical factor for regenerative myogenesis in muscle satellite cells. Our results indicate that cyclic vibration stimuli are effective in activating satellite cells and facilitate recovery from immobilization-induced oxidative myofiber atrophy through upregulation of MGF and YAP1."[304]

Carbon Dioxide Bathing

CO2 Bathing significantly promotes angiogenesis. Although the accessibility of this therapy is a bit difficult to predict currently, purchasing a CO2 Tank, paying to have it filled at a local gaseous chemical business (e.g. AirGas), & making your own CO2 Bath's would not be impossible.

[A] CO2 Bathing enhances VEGF expression in injured limbs.

"<>Background: Carbon dioxide-rich water bathing has the effect of vasodilatation, whereas it remains undetermined whether this therapy exerts an angiogenic action associated with new vessel formation.
<>Methods and results: Unilateral hindlimb ischemia was induced by resecting the femoral arteries of C57BL/J mice. Lower limbs were immersed in CO2-enriched water (CO2 concentration, 1000 to 1200 mg/L) or freshwater (control) at 37 degrees C for 10 minutes once a day. Laser Doppler imaging revealed increased blood perfusion in ischemic limbs of CO2 bathing (38% increase at day 28, $P<0.001$), whereas N(G)-nitro-L-arginine methyl ester treatment abolished this effect. Angiography or immunohistochemistry revealed that collateral vessel formation and capillary densities were increased (4.1-fold and 3.7-fold, $P<0.001$, respectively). Plasma vascular

endothelial growth factor (VEGF) levels were elevated at day 14 (18%, P<0.05). VEGF mRNA levels, phosphorylation of NO synthase, and cGMP accumulation in the CO2-bathed hindlimb muscles were increased (2.7-fold, 2.4-fold, and 3.4-fold, respectively) but not in forelimb muscles. The number of circulating Lin-/Flk-1+/CD34- endothelial-lineage progenitor cells was markedly increased by CO2 bathing (24-fold at day 14, P<0.001). The Lin-/Flk-1+/CD34- cells express other endothelial antigens (endoglin and VE-cadherin) and incorporated acetylated LDL.
<>Conclusions: Our present study demonstrates that CO2 bathing of ischemic hindlimb causes the induction of local VEGF synthesis, resulting in an NO-dependent neocapillary formation associated with mobilization of endothelial progenitor cells."[304.1]

[B] CO2 promotes adipogenesis, but I do not believe this will be of concern to athletes who are lean and highly physically conditioned, and regarding CO2 Bathing, I believe the duration of CO2 exposure will be too minimal to cause significant deleterious consequences.

"<>In the this issue of the Journal, Kikuchi and colleagues (pp. 570–580) show that elevated ambient CO2 (i.e., 10% or 7.5% compared with 5%) dose dependently accelerates differentiation of human subcutaneous and visceral preadipocytes in culture (i.e., adipogenesis) (9). This held true under normoxia and hypoxia, under neutral (pH 7.4) and acidic (pH 7.1) extracellular conditions, and during sustained, intermittent (30 min every h, 6 h/d, for 4 d), or transient (6 continuous h/d for 4 d) hypercapnia.
<>By contrast, hypercapnia did not impact adipocyte hypertrophy. The authors provide evidence that CO2 drives adipogenesis through a pathway involving soluble adenylyl cyclase (sAC)-dependent production of cyclic adenosine monophosphate (cAMP). Specifically, hypercapnia-induced cAMP activates cAMP response element binding protein (CREB), in turn promoting activation of the proadipogenic transcription factors PPARγ and CCAAT/enhancer binding protein β.
<>The authors also provide evidence that two additional cAMP effectors that have previously been implicated in adipogenesis, protein kinase A and exchanger protein directly activated by cAMP, are also activated by hypercapnia in a sAC-dependent manner, and also contribute to hypercapnia-induced adipogenesis. With regard to translational relevance, the authors propose that this pathway may put a deleterious positive feedback loop in motion during OSA: hypercapnia accelerates adipogenesis, increasing fat mass and hypoventilation, thereby exacerbating hypercapnia."[304.2]

Bloodletting (Whole Blood Donation)

A rather interesting modality, quite *exhausting,* but having an application in angiogenesis, do make sure to alternate donation arms! A word of wisdom, ensure you are hydrated with a sugary drink before you donate, you may suffer a bad reaction, also make sure that you remind your phlebotomist to be gentle with the insertion of the intimidatingly large needle that will be used to avoid damaging the nerves that lie below your blood vessels. After bloodletting you should apply a significant amount of vibration to your damaged

Median cubital vein with a car polisher, to ensure angiogenesis proceeds rapidly and efficiently.

"<>Anemia may accelerate angiogenesis in ischemic organs through its ability to augment tissue hypoxia-induced generation of several known angiogenic factors and to increase erythropoietin levels, which are also potently angiogenic. We examined the effect of controlled phlebotomy (bloodletting) on blood flow in a mouse ischemic leg model. We ligated the right femoral artery of BALB/c mice. In the phlebotomy group, 200 microl of blood were drawn from the tail vein once a week.
<>After 4 wk, blood flow in the ischemic leg was significantly better in the phlebotomy group (flow ratio of the ischemic to nonischemic leg, 0.87 + or - 0.04) than the control group (0.59 + or - 0.05, P < 0.05), and capillary density was significantly higher. Repeated phlebotomy increased serum erythropoietin levels as well as the expression of hypoxia-inducible transcription factor-1alpha and vascular endothelial growth factor and both the expression and activity of Akt and endothelial nitric oxide synthase (eNOS) in ischemic legs.
<>Treatment with wortmannin or N(omega)-nitro-l-arginine methyl ester significantly attenuated the phlebotomy-induced improvement of blood flow. In addition, fluorescence-activated cell sorting analysis revealed an increase in circulating peripheral endothelial progenitor cells in the phlebotomy group, and treatment with AMD3100, a specific inhibitor of the chemokine receptor CXCR4, blocked the beneficial effect of phlebotomy.
<>These findings suggest that repeated phlebotomy improves blood flow in ischemic legs through an angiogenic action that involves the Akt/eNOS pathway, endothelial progenitor cell mobilization, and their complicated cross talk. An adequately controlled phlebotomy might be one method by which to induce therapeutic angiogenesis."[305]

Cupping Therapy

An ancient Chinese Traditional Medicine technique that may aid in cancer resiliency by way of angiogenic lymphatic vessel growth. Lymph (the fluid that flows in the Lymphatic System) is unresearched regarding its effects on myogenesis, but I am nearly certain it will accelerate or magnify the process. It is my hypothesis, although I am certain I am not the only one to notice the connection, that the "Meridian System" may in fact be an archaic representation of the Lymphatic System.

[A] "<>Lymphatic vessels regulate the transport of tissue fluid and facilitate the absorption of macromolecules from peripheral tissues. Proper recirculation of fluids and cells via the effective transportation of lymph is required to maintain an organism's homeostasis. Lymphatic vessels are also key routes of immune cell transport from tissues to regional lymph nodes during an immune response. Under physiological conditions, the lymph contains over 1000 protein types and many other biomolecules, including a combination of plasma filtrate and soluble molecules produced by the peripheral tissues. The lymph also carries insoluble material to the draining lymph nodes, including specific

antigens, bacteria, and viruses. The concentrations of most of the transported endogenous and exogenous proteins are markedly decreased between the afferent and draining lymph, indicating they are effectively captured in the lymph nodes"[305.0]

[B] "<>Background: The aim of the study was to investigate the regulatory mechanism of local lymphatic reconstruction after cupping therapy in a mouse model.
Materials and methods: The lymphatic reconstruction process in the mouse tail after cupping therapy as well as the expression levels of the vascular endothelial identification molecule CD34, prospero homeobox protein 1 (PROX1), and lymphatic vessel endothelial hyaluronan receptor 1 (LYVE-1) were investigated for a duration of 4 days through immunohistochemistry experiments.
<>Results: On day 1 after cupping therapy, the CD34+ and LYVE-1+ cell densities were significantly increased, and the formed CD34+LYVE-1+ tubular structure started to express PROX1. This was followed by a decrease in both the CD34+ and LYVE-1+ stem cell densities to basal levels on the second day after cupping therapy. Both the CD34+ and LYVE-1+ cell densities subsequently increased again on the third day after cupping therapy. The increase in the LYVE-1+ density was accompanied by tubular structure formation, which is characteristic of lymphangiogenesis. In addition, the colocalization of CD34+ and LYVE-1+ cells by immunohistochemistry suggests that the CD34+ stem cells differentiated into new lymphatic endothelial cells.
<>Conclusions: Our findings indicate that the mechanism underlying the therapeutic effect of cupping therapy involves upregulation of vascular and lymphatic endothelial markers (CD34+, LYVE-1+, and CD34+LYVE-1+) in local tissues, which in turn promotes local new lymphatic vessel formation through the expression of PROX1."[305.1]

Hypothermic Angiogenic Sensitization (HAS)

In an intriguing research paper by Pierre Lemieux, Emilie Roudier, and Olivier Birot, it is posited, and evidence is given towards the potential therapeutic potential of exposing skeletal muscle endothelial cells (SMECS) to hypothermia followed by rewarming to sensitize them towards increased migratory potential. If this study is accurate then it may be possible to enhance skeletal muscle capillary growth by preconditioning them with Hypothermia Therapy prior to exercise, or hours before exercise. If the exercise performed after hypothermic preconditioning involves occlusion, and Hyperthermia Therapy is utilized post-exercise, this may result in a significant increase in adaptive angiogenesis, although to best mimic this study which describes many hours of cold and rewarming periods, I would suggest AM Warmups / Extended Hypothermia Therapy (30-60 Minute Ice Bath), and PM Programmed Exercise / Hyperthermia Therapy, thus allowing ample time between Thermal Therapies to allow the body to reach homeostasis.
Now there must be a large difference between localized HAS, and systemic HAS, that being muscular angiogenesis versus possibly muscular *and* neurological-cardiovascular angiogenesis. Soaking your arms in a kitchen sink ice bath for the previously mentioned

time periods in the morning before an evening angiogenic arm workout seems intelligent and plausibly effective towards the magnification of exercise-induced angiogenesis.

I believe two accurate descriptors for this new science of cycling heat and cold stress should be *Thermal Therapy Cycling*, and *Hypothermic Angiogenic Sensitization*, therefore I have coined these terms for simplicity of understanding.

One complexity of this therapy that has not been covered is that I do not know the effect that inhibiting angiogenesis would be 12, 24, or 48h after an angiogenic workout. The process of angiogenesis is considered to take weeks, and this may perturb its completion, wherein new capillary sprouts connect with one another to form blood vessel networks, and it may be possible that HAS Therapy may promote such a strong angiogenic response following reheating and stimulation of growth factors that it may overcome frequent but short duration angiostasis.

Finally, HAS Therapy appears to only promote Endothelial Cell Migration, meaning it will likely only increase the *density* and or function of preexisting muscle capillaries (Capillary Hypertrophy) which will not enhance myogenesis, but may enhance strength-endurance. It may be possible though to enhance both Endothelial Cell Migration and Proliferation by combining infrequent HAS Therapy, rewarming, and Occlusion Training, or Deep-Tissue Massage. If Hypothermia Therapy is utilized in the evening hours following early morning angiogenic training, or to reverse this, if morning Hypothermia Therapy is utilized followed by late evening angiogenic training, I believe Capillary Hypertrophy will still proceed, even if traditional angiogenesis is halted, as it is my idea that angiogenesis shares many similarities to the timespan process of myogenesis, meaning that Capillary Hypertrophy is to be considered an early adaptive process, whereas Capillary Hyperplasia is to considered a late adaptive process.

"<>The skeletal muscle tissue can adapt to exercise and environmental stressors with a remarkable plasticity. Prolonged cold stress exposure has been associated to increased skeletal muscle capillarization. Angioadaptation refers to the coordinated molecular and cellular processes that influence the remodeling of skeletal muscle microvasculature. Two cell types are central to angioadaptation: the myocytes, representing an important source of angiokines; and the skeletal muscle endothelial cell (SMECs), targets of these angiokines and main constituents of muscle capillaries. The influence of cold stress on skeletal muscle angioadaptation remains largely unknown, particularly with respect to myocyte-specific angiokines secretion or endothelial cell angioadaptive responses. Here, we use an in vitro model to investigate the impact of cold stress (28°C versus 37°C) on C2C12 myotubes and SMECs.

<>Our main objectives were to evaluate: 1) the direct impact of cold stress on C2C12 cellular expression of angiokines and their release in the extracellular environment; 2) the indirect impact of cold stress on SMECs migration via these C2C12-derived angiokines; and 3) the direct effect of cold stress on SMECs angioadaptive responses, including migration, proliferation, and the activation of the vascular endothelial growth factor receptor-2 (VEGFR2).

<>Cold stress reduced the secretion of angiokines in C2C12 myotubes culture media irrespective their pro-angiogenic or angiostatic nature. In SMECs, cold stress abrogated

cell proliferation and reduced the activation of VEGFR2 despite a greater expression of this receptor.
<>Finally, SMECs pre-conditioned to cold stress displayed an enhanced migratory response when migration was stimulated in rewarming conditions. Altogether our results suggest that cold stress may be overall angiostatic. However, cold stress accompanied by rewarming may be seen as a pro-angiogenic stressor for SMECs. This observation questions the potential for using pre-cooling in sport-performance or therapeutic exercise prescription to enhance skeletal muscle angioadaptive responses to exercise."
↓ continued
"<>Here, we evaluated how cold stress per se might impact endothelial cells by modulating the release of angiokines from muscle cells, and we compared this indirect effect to the direct exposure of endothelial cells to cold. Our results identified cold stress as a powerful tool to hinder the secretion of angiokines by myotubes. Yet, this did not shift angioadaption. Pro-angiogenic and angiostatic molecules were equally affected, and the secretome from cold-treated myotubes had no impact on endothelial cell migration.
<>Conversely, the direct exposure of primary skeletal muscle endothelial cells to cold blunted their proliferation despite higher protein levels of VEGFR2. Interestingly, when pre-cooled endothelial cells were cultured back into a warm environment, they proliferated similarly to control warm pre-conditioned cells but displayed a stronger migratory response to pro-angiogenic stimuli. This pre-cooling effect contrasts with direct cold exposure. If cold "freezes" the myotubes-specific secretion of angiokines and SMECs proliferation, pre-cooling could "prime" endothelial cells for greater migratory responsiveness.
<>Based on these observations, cold could then exert an intriguing dichotomic angioadaptive effect, from "angiostatic freeze to angiogenic move" during cold-rewarming cycles. Although being appealing, this perspective is however based on SMECs migration in vitro in a Boyden chamber assay. Future research should investigate the pro-angiogenic potential of pre-cooling conditioning by using more functional assays such as evaluating SMECs migration and vascular tube formation in a tri-dimensional matrigel assay in vitro and in vivo."
↓ continued
"Here, we suggest that cold could also be considered as a pre-exercise approach to "prime" the skeletal muscle tissue for greater exercise adaptive responses, particularly exercise-induced angiogenesis. Muscle cells might indeed secrete more VEGF-A whereas SMECs might express more VEGFR2 and show better migratory responsiveness. This potential of cold stress to exacerbate the pro-angiogenic stimulus of exercise shares similitudes with the strategy of hypoxia training."[305.2]

[See: Anti-Inflammation Cycle Modalities: Heat Pad Therapy]

[See: Photobiomodulation Therapy]

Bioavailability Enhancers

These chemicals are also termed as ‘absorption enhancers’ which are functional excipients included in formulations to improve the absorption of a pharmacologically active drug. The term ‘bioavailability enhancer’ was first coined by Indian scientists at the Regional Research Laboratory, Jammu (RRL, now known as Indian Institute of Integrative Medicine, Jammu), who discovered and scientifically validated Piperine as the world's first bioavailability enhancer in 1979.”[306]

Bioavailability Enhancers are a wave of the future to be certain, but increases to the absorption of a phytochemical, ergogenic, or pharmaceutical can have negative side effects due to the accumulation of toxic levels of the aforementioned compounds.

Piperine

Combining Piperine with your supplements, primarily phytochemicals, is an excellent way to enhance their bioavailability, unfortunately it is neurotoxic by way of cytotoxicity. To combine Piperine with Curcumin, the potential dysbiosis-inducing agent, may hold great value for treating cancer, but for health-proofing yourself it seems unwise, as the brain is the most important organ in the human body. Some may argue that the concentration of Piperine that reaches the serum if taken in small amounts will be irrelevant towards cytotoxicity, but the point remains, it is toxic.

[A] Piperine enhances bioavailability through intestinal permeability.

Piperine is an effective bioavailability enhancer through interaction with small intestine permeation.

“<>Piperine (1-Piperoyl piperidine) is a major alkaloid of Piper nigrum Linn. and Piper longum Linn. It is shown to possess bioavailability-enhancing activity with various structurally and therapeutically diverse drugs. The mechanism of enhancing the bioavailability, is, however, not understood. We hypothesize that piperine's bioavailability-enhancing property may be attributed to increased absorption, which may be due to alteration in membrane lipid dynamics and change in the conformation of enzymes in the intestine.
<>Results of membrane fluidity studies using an apolar fluorescent probe, pyrene (which measures the fluid properties of hydrocarbon core), showed an increase in intestinal brush border membrane (BBM) fluidity. Piperine also stimulated Leucine amino peptidase and Glycyl-glycine dipeptidase activity, due to the alteration in enzyme kinetics. This suggests that piperine could modulate the membrane dynamics due to its apolar nature by interacting with surrounding lipids and hydrophobic portions in the protein vicinity, which may decrease the tendency of membrane lipids to act as stearic constrains to enzyme proteins and thus modify enzyme conformation. Ultra structural studies with piperine showed an increase in microvilli length with a prominent increase in free ribosomes and ribosomes on the endoplasmic reticulum in enterocytes, suggesting that

synthesis or turnover of cytoskeletal components or membrane proteins may be involved in the observed effect.
<>In conclusion, it is suggested that piperine may be inducing alterations in membrane dynamics and permeation characteristics, along with induction in the synthesis of proteins associated with cytoskeletal function, resulting in an increase in the small intestine absorptive surface, thus assisting efficient permeation through the epithelial barrier."[307]

[B] Piperine is neurotoxic 1.

"<>The presence of piperine in a serum-free medium for 72 h markedly inhibited the neurite extension of cultured hippocampal and septal neurons under both high and low density cell culture conditions (initial cell density was 10(5) cells/cm2 and 2.5-5 x 10(3) cells/cm2, respectively). The average length of neurites decreased over a concentration range of piperine (12.5-100 microM), and the distribution of neurite population shifted towards the shorter neurite lengths whereas an increase in the soma size was observed only with high piperine concentrations (75 and 100 microM, in a high density cell culture).
<>This indicates that the piperine effect was relatively selective to the neurite extension. The neurite extension in low density cell cultures was considerably more susceptible to piperine than that in high density cell cultures (hippocampus: EC50 = 39 versus 113 microM, septum: EC50 = 48 versus 101 microM, in the low and high density cell cultures, respectively). This difference may be due to a lack of neurotrophic supports from non-neuronal cells under the low density cell culture condition. These findings suggest that piperine, in addition to its cytotoxic effect on the neuronal survival, suppresses the neurite extension in developing neurons."[308]

[B2] Piperine is neurotoxic 2.

"<>The present study investigated the selective cytotoxicity of piperine on cultured brain cells by using lactate dehydrogenase release, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium reduction, and protein content assay. Exposure to piperine induced marked injuries on cultured hippocampal neurons whereas it induced only a marginal toxicity on cultured astrocytes. The mechanism of cytotoxicity in hippocampal neurons was studied by pharmacological methods.
<>The membrane-permeable free radical scavengers, D-alpha-tocopherol and trolox, protected neurons from piperine toxicity whereas membrane-impermeable agents, superoxide dismutase and catalase, were ineffective. A lipoxygenase inhibitor, nordihydroguaiaretic acid, but not a cyclo-oxygenase inhibitor, indomethacin, attenuated piperine toxicity. We provide the first evidence that piperine induces selective neurotoxicity in vitro. Although the exact mechanism is still unclear, pharmacological evidence indicates the possible involvement of lipid peroxidation and the generation of free radicals, at least partly, through an arachidonate-lipoxygenase pathway."[309]

Common Recreational Chemicals

Alcohol (Ethanol: EtOH)

Alcohol in my hypothesis is the leading accelerator of musculoskeletal aging in humans residing in the Western world as it is so damaging to tendons and muscles in chronic amounts. Because EtOH is such a wonderful angiogenic compound and in all probability the reason for Arnold Schwarzenegger's massive biceps development (he was quite a drinker when he moved to Munich early in his early life), very low dosages should be consumed on the Pro-Inflammation Cycle. In low dosages, EtOH is a superb angiogenic antioxidant.

[A] Ethanol administered immediately pre-workout magnifies exercise-induced release of angiogenic growth factors and promotes skeletal muscle angiogenesis regardless of exercise. The dosage of ethanol used in this study resulted in a predicted 0.10% BAC, which is not suggested by me. Interestingly, ethanol appears to enhance not only VEGF, but also bFGF, and as expected, TGF-b. The increased angiogenesis resulting from ethanol use, such as in ancient, fermented drinks, clearly played a role in our behavioral & physical evolution.

"<>Moderate ethanol consumption demonstrates a protective effect against cardiovascular disease and improves insulin sensitivity, possibly through angiogenesis. We investigated whether *1*) ethanol would increase skeletal muscle growth factor gene expression and*2*) the effects of ethanol on skeletal muscle growth factor gene expression were independent of exercise-induced growth factor gene expression.
<>Female Wistar rats were used. Four groups (saline + rest; saline + exercise; 17 mmol/kg ethanol + rest; and 17 mmol/kg ethanol + exercise) were used to measure the growth factor response to acute exercise and ethanol administration. Vascular endothelial growth factor (VEGF), transforming growth factor-β_1 (TGF-β_1), basic fibroblast growth factor (bFGF), Flt-1, and Flk-1 mRNA were analyzed from the left gastrocnemius by quantitative Northern blot.
<>Ethanol increased VEGF, TGF-β_1, bFGF, and Flt-1 mRNA at rest and after acute exercise. Ethanol increased resting Flk-1 mRNA. Ethanol increased bFGF mRNA independently of exercise. These findings suggest that*1*) ethanol can increase skeletal muscle angiogenic growth factor gene expression and *2*) the mechanisms responsible for the ethanol-induced increases in VEGF, TGFβ_1, and Flt-1 mRNA appear to be different from those responsible for exercise-induced regulation. Therefore, these results provide evidence in adult rat tissue that the protective cardiovascular effects of moderate ethanol consumption may result in part through the increase of angiogenic growth factors."[311]

[B] Ethanol enhances angiogenesis in low dosages when administered either chronically or subchronically (18h, 6h, etc.). The ideal dosage reference is 0.125g x kg, with the difference in angiogenic potential resulting from 0.125g x kg versus 0.25g x kg being minimal (39% vs 53%).

"<>Alcohol abuse has a negative impact on human health; however, epidemiological studies show that moderate consumption of ethanol (EtOH) reduces the risk of coronary heart disease, sudden cardiac death, and ischemic stroke. The mechanisms for these reductions in cardiovascular disease are not well established. Using cultured coronary artery vascular smooth muscle cells, we found that moderate levels of EtOH (10 and 20 mM) caused dose-related increases in both vascular endothelial growth factor (VEGF) mRNA (Northern blot) expression (1.9- and 2.6-fold) and VEGF protein (ELISA) expression (19 and 68%) compared with control ($P < 0.05$).
<>EtOH at 0.25 g. kg(-1). day(-1) (7 days) increased VEGF mRNA expression by 1.48-fold over control, and increased vessel length density from 3.9 +/- 0.7 (control) to 6.0 +/- 0.3 mm/mm(2) ($P < 0.05$) in chick chorioallantoic membrane (CAM). We conclude that moderate levels of ethanol can induce VEGF expression and stimulate angiogenesis in chick CAM. Therefore, the results provide a theoretical basis for speculating that the cardiovascular-protective effects of moderate alcohol consumption may be partly mediated through VEGF-induced angiogenesis.
<>Administration of ethanol at 0.125 and 0.25 $g \cdot kg^{-1} \cdot day^{-1}$ for 7 days caused VLD to increase by 39% ($n = 6$; $P< 0.05$) and 53% ($n = 6$; $P < 0.05$), respectively, compared with the control group.
<>We have concerns that exposing CAVSMC to 20 mmol/l ethanol for 18 h could be too long compared with moderate alcohol consumption in human settings. However, Fig. 4 A shows that ethanol levels in the media cultured with CAVSMC significantly decreased >15% after 12 h incubation. In addition, exposing CAVSMC to 20 mmol/l ethanol for 6 h significantly increased VEGF protein levels in media by 27%, compared with control ($P < 0.01$), demonstrating that even a comparatively short exposure can induce VEGF expression."[312]

[C] Ethanol enhances angiogenesis in mice fed a high fat diet.

"<>Endothelial progenitor cells (EPCs) and monocytic cells from bone marrow (BM) can be recruited to the injured endothelium and contribute to its regeneration. During metabolic diseases such as obesity and diabetes, progenitor cell function is impaired. Several studies have shown that moderate alcohol consumption prevents the development and progression of atherosclerosis in a variety of animal/mouse models and increases mobilization of progenitor cells. Along with these studies, we identify ethanol at low concentration as therapeutic tool to in vitro expand progenitor cells in order to obtain an adequate number of cells for their use in the treatment of cardiovascular diseases.
<>We evaluated the effects of ethanol on the phenotype of BM-derived cells from mice fed with high-fat diet (HFD). HFD did not induce changes in weight of mice but induced metabolic alterations. HFD feeding increased the differentiation of monocytic progenitors but not EPCs. Whereas ethanol at 0.6% is able to increase monocytic progenitor differentiation, 1% ethanol diminished it.
<>Furthermore, ethanol at 0.6% increased the ability of progenitor cells to promote in vivo angiogenesis as well as secretome of BM-derived cells from mice fed with HFD, but not in mice fed normal diet. In conclusion, ethanol at low concentration is able to

increase angiogenic abilities of progenitor cells from animals with early metabolic alterations."[313]

[D] Even moderate dosages of alcohol use cause increased cerebral angiogenesis, and this effect is surely to be magnified through endurance training, but I do not suggest ever using more than 0.5g / kg of EtOH per day to protect your musculoskeletal system.

"<>As reported previously, daily gavage feeding with either 0.7 or 2.8 g/kg/day ethanol once a day for 8 weeks did not significantly change body weight, MABP, heart rate, and fasting glucose level. However, 8-week feeding with 0.7 g/kg/day ethanol significantly increased vessel density and the number of branches in the cerebral cortex and subcortical area under physiological conditions. Consistently, 0.7 g/kg/day ethanol feeding significantly upregulated VEGF-A and VEGFR2 in the cerebral cortex. In contrast, 8-week feeding with 2.8 g/kg/day ethanol did not alter either vessel density or the number of branches in the cerebral cortex under physiological conditions. It only slightly but significantly reduced the number of branches in the subcortical area. However, 2.8 g/kg/day ethanol feeding did not significantly alter either VEGF-A or VEGFR2 in the cerebral cortex."[313.1]

[E] Chronic alcohol use decreases Cannabinoid-1 receptor binding. This decrease in CB1r binding may enhance the effectiveness of THC as a CB1 agonist by reducing desensitization processes, thus explaining the binge drinking many cannabis users engage in.

"<>Brain cannabinoid CB1 receptors contribute to alcohol-related behaviors in experimental animals, but their potential role in humans with alcohol dependence is poorly understood. We measured CB1 receptors in alcohol dependent patients in early and protracted abstinence, and in comparison with control subjects without alcohol use disorders, using positron emission tomography and [18F]FMPEP-d2, a radioligand for CB1 receptors.
<>We scanned 18 male in-patients with alcohol dependence twice, within 3–7 days of admission from ongoing drinking, and after 2–4 weeks of supervised abstinence. Imaging data were compared with those from 19 age-matched healthy male control subjects. Data were also analyzed for potential influence of a common functional variation (rs2023239) in the CB1 receptor gene (CNR1) that may moderate CB1 receptor density.
<>On the first scan, CB1 receptor binding was 20–30% lower in patients with alcohol dependence than in control subjects in all brain regions and was negatively correlated with years of alcohol abuse. After 2–4 weeks of abstinence, CB1 receptor binding remained similarly reduced in these patients. Irrespective of the diagnostic status, C allele carriers at rs2023239 had higher CB1 receptor binding compared with non-carriers. Alcohol dependence is associated with a widespread reduction of cannabinoid CB1 receptor binding in the human brain and this reduction persists at least 2–4 weeks into abstinence. The correlation of reduced binding with years of alcohol abuse suggests an involvement of CB1 receptors in alcohol dependence in humans."[314]

[F] Chronic Alcohol use upregulates NMDA receptor activity in the spine, explaining why during alcohol withdrawal we experience increased muscle force generation (my hypothesis).

"<>Chronic ethanol consumption produces painful neuropathy for which there is no reliably successful therapy, largely due to a lack of understanding of the central mechanisms that underlie the development of the neuropathic pain-like state induced by chronic ethanol treatment.
<>The aim of this study was to investigate what mechanisms contribute to the neuropathic pain-like state induced by chronic ethanol treatment in rats. Mechanical hyperalgesia was clearly observed during ethanol consumption and even after ethanol withdrawal, and lasted for 14 weeks. This hyperalgesia was significantly attenuated by repeated i.p. injection of ifenprodil, a selective NR2B subunit-containing NMDA receptor antagonist. Under these conditions, mRNA and protein levels of NR1, NR2A and NR2B subunits did not change in the spinal cord of chronic ethanol-fed rats.
<>Interestingly, phosphorylated-Ser-1303 NR2B (p-Ser1303-NR2B) subunit was significantly increased in the spinal cord of chronic ethanol-fed rats, whereas p-Tyr1472-NR2B was not affected in the superficial spinal dorsal horn of ethanol-fed rats. These findings suggest that spinal p-Ser1303-NR2B plays a significant role in the development of the ethanol-dependent neuropathic pain-like state in rats."[314.1]

[G] Chronic ethanol halts myogenesis.

"The effects of EtOH on skeletal muscle have been studied in experimental animals or on biopsies from alcoholic patients. However, alterations in skeletal muscle from alcoholic patients could be secondary to the effects of EtOH on the nervous system. In this study, by assaying the action of EtOH on primary skeletal muscle cell cultures, we provide evidence of its direct effect on skeletal muscle proliferation and differentiation. The results indicate that EtOH: (1) significantly inhibits skeletal muscle cell proliferation at the beginning of the proliferation phase; (2) delays skeletal muscle differentiation, shown by the significant changes in the evolution of the percentage of the creatine kinase isozymes; (3) has no significant effect on skeletal muscle DNA or protein content during the proliferation phase."[315]

[H] Alcohol damages tendons.

"<>Forty-seven rats were randomly assigned to either ethanol or control groups. Progressively increasing concentrations of ethanol combined with glucose were administered to these rats in their drinking water. After 1 week, the Achilles tendon of each rat was injured proximal to its insertion on the calcaneus. All rats were euthanized at 4 weeks. The tendons were evaluated both histologically and biomechanically. The histologic examination of these tendons was done using a semi-quantitative 4-point scale to rate cell morphology, the degree of ground substance staining, collagen organization,

and vascular changes. Load to failure (N) strength was obtained with biomechanical testing.
<>Tendon failure loads were lower in the ethanol group (31.6 +/- 8.8 N) than in the control group (39.7 +/- 8.2 N) (P = 0.04). Histologic tenocyte scores were higher in the ethanol group (1.90 +/- 0.73) than the control group (0.9 +/- 0.73) (P = 0.01).
<>Conclusion: Ethanol ingestion resulted in abnormal tenocyte morphology, disorganized collagen bundles with a tendency toward increased tenocyte number, and neovascularization 3 weeks after the tendon injury indicating delayed and abnormal healing. The healing tendons in the alcohol treated group failed at statistically lower loads than the control group."[316]

[I] Very low concentrations of ethanol may enhance anabolism through Phospholipase D.

"<>Ethanol (EtOH) decreases muscle protein synthesis, and this is associated with reduced mammalian target of rapamycin complex (mTORC)1 and increased mTORC2 activities. In contrast, phospholipase D (PLD) and its metabolite phosphatidic acid (PA) positively regulate mTORC1 signaling, whereas their role in mTORC2 function is less well defined. Herein, we examine the role that PLD and PA play in EtOH-mediated mTOR signaling.
<>Methods: C2C12 myoblasts were incubated with EtOH for 18 to 24 hours. For PA experiments, cells were pretreated with the drug for 25 minutes followed by 50-minute incubation with PA in the presence or absence of EtOH. The phosphorylation state of various proteins was assessed by immunoblotting. Protein-protein interactions were determined by immunoprecipitation and immunoblotting.
<>Results: PA levels and PLD activity increased in C2C12 myocytes exposed to EtOH (100 mM). Increased PLD activity was blocked by inhibitors of AMP-activated protein kinase (AMPK) (compound C) and phosphoinositide 3-kinase (PI3K) (wortmannin). Likewise, suppression of PLD activity with CAY10594 prevented EtOH-induced Akt (S473) phosphorylation. PLD inhibition also enhanced the binding of Rictor to mSin1 and the negative regulatory proteins Deptor and 14-3-3. Addition of PA to myocytes decreased Akt phosphorylation, but changes in mTORC2 activity were not associated with altered binding of complex members and 14-3-3. PA increased S6K1 phosphorylation, with the associated increase in mTORC1 activity being regulated by reduced phosphorylation of AMPKα (T172) and its target tuberous sclerosis protein complex (TSC)2 (S1387). This resulted in increased Rheb and RagA/RagC GTPase interactions with mTOR, as well as suppression of mTORC2.
<>Conclusions: EtOH-induced increases in PLD activity and PA may partially counterbalance the adverse effects of this agent. EtOH and PA regulate mTORC1 via a PI3K/AMPK/TSC2/PLD signaling cascade. PA stimulates mTORC1 function and suppresses activation of mTORC2 as part of an mTORC1/2 feedback loop."[317]

[I2] Phospholipase D hypertrophies muscle.

"<>mTOR is a major actor of skeletal muscle mass regulation in situations of atrophy or hypertrophy. It is established that Phospholipase D (PLD) activates mTOR signaling, through the binding of its product phosphatidic acid (PA) to mTOR protein. An influence of PLD on muscle cell size could thus be suspected. We explored the consequences of altered expression and activity of PLD isoforms in differentiated L6 myotubes. Inhibition or down-regulation of the PLD1 isoform markedly decreased myotube size and muscle specific protein content. Conversely, PLD1 overexpression induced muscle cell hypertrophy, both in vitro in myotubes and in vivo in mouse gastrocnemius.
<>In the presence of atrophy-promoting dexamethasone, PLD1 overexpression or addition of exogenous PA protected myotubes against atrophy. Similarly, exogenous PA protected myotubes against TNFα-induced atrophy. Moreover, the modulation of PLD expression or activity in myotubes showed that PLD1 negatively regulates the expression of factors involved in muscle protein degradation, such as the E3-ubiquitin ligases Murf1 and Atrogin-1, and the Foxo3 transcription factor. Inhibition of mTOR by PP242 abolished the positive effects of PLD1 on myotubes, whereas modulating PLD influenced the phosphorylation of both S6K1 and Akt, which are respectively substrates of mTORC1 and mTORC2 complexes. These observations suggest that PLD1 acts through the activation of both mTORC1 and mTORC2 to induce positive trophic effects on muscle cells. This pathway may offer interesting therapeutic potentialities in the treatment of muscle wasting."[318]

[J] Alcohol reduces mTORC1 but enhances mTORC2 in myoblasts. [See: Other Myogenic Proteins: mTORC2]

"<>Background: The mammalian target of rapamycin (mTOR) kinase controls cell growth, proliferation, and metabolism through 2 distinct multiprotein complexes, mTORC1 and mTORC2. We reported that alcohol (EtOH) inhibits mTORC1 activity and protein synthesis in C2C12 myoblasts. However, the role that mTORC2 plays in this process has not been elucidated. In this study, we investigated whether mTORC2 functions as part of a feedback regulator in response to EtOH, acting to maintain the balance between the functions of Akt, mTORC2, and mTORC1.
<>Methods: C2C12 myoblasts were incubated with EtOH for 18 to 24 hours. Levels of various mTORC2 proteins and mRNA were assessed by immunoblotting and real-time PCR, respectively, while protein-protein interactions were determined by immunoprecipitation and immunoblotting. An in vitro mTORC2 kinase activity assay was performed using Akt as a substrate. The rate of protein synthesis was determined by (35) S-methionine/cysteine incorporation into cellular protein.
<>Results: EtOH (100 mM) increased the protein and mRNA levels of the mTORC2 components rictor, mSin1, proline-rich repeat protein 5, and Deptor. There was also an increased association of these proteins with mTOR. EtOH increased the in vitro kinase activity of mTORC2, and this was correlated with decreased binding of rictor with 14-3-3 and Deptor. Reduced rictor phosphorylation at T1135 by EtOH was most likely due to decreased S6K1 activity. Knockdown of rictor elevated mTORC1 activity, as indicated by increased S6K1 phosphorylation and protein synthesis. Likewise, there were

decreased amounts and/or phosphorylation levels of various mTORC1 and mTORC2 components including raptor, proline-rich Akt substrate 40 kDa, mSin1, Deptor, and GβL. Activated PP2A was associated with decreased Akt and eukaryotic elongation factor 2 phosphorylation. Collectively, our results provide evidence of a homeostatic balance between the 2 mTOR complexes following EtOH treatments in myoblasts.
<>Conclusions: EtOH increased the activity of mTORC2 by elevating levels of various components and their interaction with mTOR. Decreased rictor phosphorylation at T1135 acts as mTORC1-dependent feedback mechanisms, functioning in addition to the insulin receptor substrate-I/PI3K signaling pathway to regulate protein synthesis."[319]

[K] Chronic Alcohol withdrawal enhances brain cell growth during long duration abstinence, explaining the possible adaptation and addictive nature of infrequent but severe "binge drinking".
"<>This study is the first to show that chronic ethanol continues to alter neurogenesis in the adult rat hippocampus weeks after the cessation of ethanol. Specifically, we report for the first time that neurogenesis was increased over twofold at 5 weeks into abstinence. Alcohol dependence induced a fourfold burst in cell proliferation at day 7 of abstinence that is specific to the dentate gyrus SGZ, a region containing NPCs. After the burst in cell proliferation, evidenced by increased BrdU-labeled cells, was an increase in DCX-IR at day 14. This increase in DCX-IR lagged 1 week behind the increase in cell proliferation, which suggests that alcohol dependence also increased neurogenesis.
<>Furthermore, we observed that the cells produced at day 7 survive at least 28 d, such that the number of BrdU+ cells remains increased at day 35. Analysis of cell phenotype at day 35 (day 7 + 28 d) showed that the newborn cells in the ethanol-exposed animals differentiated similar to controls.
<>Thus, neurogenesis was increased at 5 weeks in abstinence and was likely attributable to the burst in cell proliferation at day 7. Together, the data suggest that ethanol decreases neurogenesis during intoxication, consistent with our previous work, and as we report for the first time, ethanol increases neurogenesis during abstinence after alcohol dependence."[320]

[K2] Binge drinking causes muscle fibrosis.

"<>Binge Drinking (BD) corresponds to episodes of ingestion of large amounts of ethanol in a short time, typically ≤2 h. BD occurs across all populations, but young and sports-related people are especially vulnerable. However, the short- and long-term effects of episodic BD on skeletal muscle function have been poorly explored. Young rats were randomized into two groups: control and episodic Binge-Like ethanol protocol (BEP) (ethanol 3 g/kg IP, 4 episodes of 2-days ON-2-days OFF paradigm). Muscle function was evaluated two weeks after the last BEP episode.
<>We found that rats exposed to BEP presented decreased muscle strength and increased fatigability, compared with control animals. Furthermore, we observed that skeletal muscle from rats exposed to BEP presented muscle atrophy, evidenced by reduced fiber size and increased expression of atrophic genes. We also observed that BEP induced

fibrotic and inflammation markers, accompanied by mislocalization of nNOSμ and high levels of protein nitration.
<>Our findings suggest that episodic binge-like ethanol exposure alters contractile capacity and increases fatigue by mechanisms involving atrophy, fibrosis, and inflammation, which remain for at least two weeks after ethanol clearance. These pathological features are common to several neuromuscular diseases and might affect muscle performance and health in the long term."[320.1]

[L] Low dose Alcohol promotes lifespan.

"Alcoholic beverages are consumed widely throughout the world. While the harmful effects of alcoholism are well recognized, the beneficial effects of moderate alcohol consumption to human health remain debatable. In this study, we investigated the effects of long-term ethanol exposure on nematode Caenorhabditis elegans worms. At high concentrations (≥ 4%), ethanol significantly impaired mobility, reduced fertility, and shortened lifespan. Interestingly, at low concentrations (1-2%), it extended lifespan, accompanied with a slower decline of mobility during aging, although it slightly impaired development, fertility, and chemotaxis. The lifespan-prolonging effects of ethanol at the low concentrations were seen in normal worms exposed to ethanol from egg, young larva, and young adult stages but were not observed in age-1 and sir-2.1 mutant worms. Our study demonstrated hormetic effects of ethanol and further established C. elegans as a suitable animal model to study ethanol related problems."[321]

[M] Low Dose Alcohol promotes Glymphatic function, which is associated with molecular waste (amyloid) clearance. Thus, low dose Alcohol may prevent the development of Alzheimer's Disease / Dementia. In this study the alcohol was administered once daily, and withdrawal from the low-dosage produced the enhanced glymphatic function, whereas in low-dose chronically administered alcohol, it took around thirty-days for the glymphatic system benefits to appear.

"<>Prolonged intake of excessive amounts of ethanol is known to have adverse effects on the central nervous system (CNS). Here we investigated the effects of acute and chronic ethanol exposure and withdrawal from chronic ethanol exposure on glymphatic function, which is a brain-wide metabolite clearance system connected to the peripheral lymphatic system. Acute and chronic exposure to 1.5 g/kg (binge level) ethanol dramatically suppressed glymphatic function in awake mice. Chronic exposure to 1.5 g/kg ethanol increased GFAP expression and induced mislocation of the astrocyte-specific water channel aquaporin 4 (AQP4), but decreased the levels of several cytokines. Surprisingly, glymphatic function increased in mice treated with 0.5 g/kg (low dose) ethanol following acute exposure, as well as after one month of chronic exposure.
<>Low doses of chronic ethanol intake were associated with a significant decrease in GFAP expression, with little change in the cytokine profile compared with the saline group. These observations suggest that ethanol has a J-shaped effect on the glymphatic system whereby low doses of ethanol increase glymphatic function. Conversely, chronic

1.5 g/kg ethanol intake induced reactive gliosis and perturbed glymphatic function, which possibly may contribute to the higher risk of dementia observed in heavy drinkers."[322]

[N] Low dose Alcohol is an immunostimulant, possibly through activating PPARy, a protein that is associated with macrophage function and mitochondrial biogenesis.

"<>A series of experiments was performed to assess the alterations in immune status in vivo that are associated with differences in the amount and duration of ethanol intake. Using a nonspecific delayed cutaneous hypersensitivity-like response to the intradermal injection of phytohemagglutinin, the area of induration (skin test response) was significantly enhanced ($p = 0.008$) after low-dose ethanol (0.5 g/kg) administered daily by gastric gavage for 5 days. High-dose ethanol (6.0 g/kg) significantly diminished this response ($p = 0.03$). Using an experimental model of Mycobacterium bovis hepatitis, the host immune response was also altered in a biphasic manner after chronic, 28-day ethanol consumption.
<>With this model 0.43 ± 0.03 g/kg/day (mean ± SEM) of ethanol (low dose) was associated with a 40% improvement in the removal of the organisms from liver tissue ($p = 0.002$). High dose (12.1 ± 0.5 g/kg/day) impaired removal, resulting in a 55% increase in the number of viable organisms ($p = 0.001$). The levels of three cytokines, MIF, TNF-α, and IL-2, known to be involved in the modulation of the host response to mycobacterial infections, were measured in sera after the infection. The serum levels of these cytokines in response to infection did not correlate with this biphasic response to different alcohol dose levels."[323]

[O] Low Dose Alcohol protects neurons from hypoxia (strokes) by activating PPARy.

"<>C57BL/6 J mice were fed a liquid diet without or with 1% alcohol for 8 weeks, orally treated with rosiglitazone (20 mg/kg/day), a peroxisome proliferator-activated receptor gamma (PPARγ)-selective agonist, or GW9662 (3 mg/kg/day), a selective PPARγantagonist, for 2 weeks. The mice were subjected to unilateral middle cerebral artery occlusion (MCAO) for 90 minutes. Brain injury, DNA fragmentation and nuclear PPARγ protein/activity were evaluated at 24 hours of reperfusion. We found that the brain injury and DNA fragmentation were reduced in 1% alcohol-fed mice compared to nonalcohol-fed mice. Rosiglitazone suppressed the brain injury in nonalcohol-fed mice, but didn't alter the brain injury in alcohol-fed mice. In contrast, GW9662 worsened the brain injury in alcohol-fed mice, but didn't alter the brain injury in nonalcohol-fed mice.
<>Nuclear PPARγ protein/activity at peri-infarct and the contralateral corresponding areas of the parietal cortex was greater in alcohol-fed mice compared to nonalcohol-fed mice. Using differentiated catecholaminergic (CATH.a) neurons, we measured dose-related influences of chronic alcohol exposure on nuclear PPARγ protein/activity and the influence of low-dose alcohol exposure on 2-hour oxygen-glucose deprivation (OGD)/24-hour reoxygenation-induced apoptosis.
<>We found that low-dose alcohol exposure increased nuclear PPARγ protein/activity and protected against the OGD/reoxygenation-induced apoptosis. The beneficial effect of

low-dose alcohol exposure on OGD/reoxygenation-induced apoptosis was abolished by GW9662."[324]

[P] Acute Alcohol exposure in humans dislocates a protein called RACK1, which promotes neurogenesis in the Dorsomedial Striatum, with this effect degrading permanently when Alcohol is consumed everyday over a period of seven weeks (or sooner). Meaning that if you've ever spent more than a few weeks drinking every single day, this homeostatic response to Alcohol is in all likelihood no longer active, but if you have never been a frequent drinker, you may still possess this response to Alcohol, thereby meaning if you consume low-moderate dosages *every other day* (one day off to allow RACK1 to reset) you will potentially increase your intelligence through enhanced neurogenesis.

"<>Importantly, we observed that ethanol-mediated nuclear translocation of RACK1 in the hippocampus and dorsal striatum is required for ethanol to increase *BDNF* expression. In addition, we showed that in the hippocampus and in the dorsal striatum under basal conditions RACK1 forms a trimolecular complex with Fyn and the NR2B subunit of the N-methyl-d-aspartate (NMDA) receptor, which is dissociated upon ethanol exposure leading to Fyn-mediated phosphorylation of NR2B via a mechanism that requires the activation of the cAMP/PKA pathway. Importantly, the NR2B/RACK1/Fyn complex cannot be detected in the cortex, and no NR2B phosphorylation is observed upon exposure of cortical neurons to ethanol. Together, these results raise the possibility that ethanol-induced dissociation of RACK1 from its complex with Fyn and the NMDA receptor may be required for RACK1's translocation and subsequent induction of *BDNF* expression in the dorsal striatum but not in the cortex.
<>While acute ethanol intake triggers striatal *BDNF* expression, which is suggested to function as a negative regulator of further ethanol intake, we show here that this protective pathway breaks down over time, such that dorsal striatal *BDNF* becomes nonresponsive and cortical *BDNF*, which is unaltered by acute ethanol exposure, is reduced following ethanol intake."[324.1]

[P2] Alcohol withdrawal is excitotoxic through hyperactivation of the NR2B receptors located in the Limbic System. These receptors are activated through the release of Tissue-Plasminogen Activator (t-PA), a very obscure protein. Both the NR2B receptors and t-PA associate with important forms of memory, meaning that it is highly possible to stimulate limbic system memory processing through planned Alcohol withdrawal, and thereby enhance memory, if the activity of these factors is not too strong i.e., if the dosage of EtOH used is very low, resulting in little to no withdrawal-induced excitotoxicity. It appears that t-PA peaks around six hours after alcohol withdrawal and begins to fall to half its value around twenty-four hours later. It is my hypothesis that t-PA is responsible for the enhanced glymphatic function that occurs after low-dose alcohol use.

[Q] "<>Tissue-plasminogen activator (tPA), a protease implicated in neuronal plasticity and seizures, is also thought to interact with NR2B-containing NMDA receptors and

suggested to play a role in up-regulation of the NR2B subunit in response to ethanol. tPA is induced in the limbic system by chronic ethanol consumption, temporally coinciding with up-regulation of NMDA receptors. Furthermore, tPA-deficient mice have reduced NR2B, extracellular signal-regulated kinase 1/2 phosphorylation and seizures after ethanol withdrawal (EW), and tPA-mediated facilitation of EW seizures was abolished by the NR2B-specific NMDA antagonist ifenprodil. These results indicate that tPA may mediate the development of physical dependence on ethanol by regulating NR2B-containing NMDA receptors."[324.2]

[Q2] "<>Induction of long-term depression (LTD) in rat striatal slices revealed that this form of synaptic plasticity is coupled to an increased expression of tissue-plasminogen activator (t-PA) mRNA, as detected by the mRNA differential display technique. To further investigate the involvement of this gene in synaptic remodelling following striatal LTD, we recorded electrical activity from mice lacking the gene encoding t-PA (t-PA-KO) and from wild-type (WT) mice. Tetanic stimulation induced LTD in the large majority of striatal neurons recorded from WT mice. <>Conversely, LTD was absent in a significant proportion of striatal neurons obtained from mice lacking t-PA. Electrophysiological recordings obtained from hippocampal slices in the CA1 area showed that mainly the late phase of long-term potentiation (LTP) was reduced in t-PA-KO mice. Learning and memory-related behavioural abnormalities were also found in these transgenic mice. Disruption of the t-PA gene, in fact, altered both the context conditioning test, a hippocampus-related behavioural task, and the two-way active avoidance, a striatum-dependent task.
<>In an open field object exploration task, t-PA-KO mice expressed deficits in habituation and reactivity to spatial change that are consistent with an altered hippocampal function. Nevertheless, decreased rearing and poor initial object exploration were also observed, further suggesting an altered striatal function. These data indicate that t-PA plays a critical role in the formation of various forms of synaptic plasticity and memory."[324.3]

[R] Alcohol withdrawal enhances Cued Memory, which means it enhances the brains ability to recall preexisting memories during exposure to familiar stimuli associated with those memories, meaning that alcohol promotes work efficiency in jobs that involve more repetitive acts and less unconditioned acts, thus explaining why alcohol has been the choice drug of many civilizations. While Alcohol withdrawal may enhance cued memory, it suppresses contextual memory, which is a form of memory required for a greater complexity of memory recall, such as the sights, sounds, and emotions experienced when a memory was formed.

"<>Background: Alcohol affects many of the brain regions and neural processes that support learning and memory, and these effects are thought to underlie, at least in part, the development of addiction. Although much work has been done regarding the effects of alcohol intoxication on learning and memory, little is known about the effects of acute withdrawal from a single alcohol exposure.

<>Methods: We assess the effects of acute ethanol withdrawal (6 h post-injection with 4 g/kg ethanol) on two forms of fear conditioning (delay and trace fear conditioning) in C57BL/6J and DBA/2J mice. The influence of a number of experimental parameters (pre- and post-training withdrawal exposure; foreground/background processing; training strength; non-associative effects) is also investigated.
<>Results: Acute ethanol withdrawal during training had a bidirectional effect on fear conditioned responses, decreasing contextual responses and increasing cued responses. These effects were apparent for both trace and delay conditioning in DBA/2J mice and for trace conditioning in C57BL/6J mice; however, C57BL/6J mice were selectively resistant to the effects of acute withdrawal on delay cued responses.
<>Conclusions: Our results show that acute withdrawal from a single, initial ethanol exposure is sufficient to alter long-term learning in mice. In addition, the differences between the strains and conditioning paradigms used suggest that specific learning processes can be differentially affected by acute withdrawal in a manner that is distinct from the reported effects of both alcohol intoxication and withdrawal following chronic alcohol exposure. Thus, our results suggest a unique effect of acute alcohol withdrawal on learning and memory processes."[324.3.1]

[S] Alcohol increases REDD1 [See: Other Hormones (Non-Androgenic): Cortisol] in fast twitch muscle fibers likely explaining the muscle fiber specific toxicity that chronic alcohol displays.

"<>Background: The mechanism by which acute alcohol (EtOH) intoxication decreases basal muscle protein synthesis via inhibition of the Ser/Thr kinase mammalian target of rapamycin (mTOR) is poorly defined. In this regard, mTOR activity is impaired after over expression of the regulatory protein REDD1. Hence, the present study assessed the ability of REDD1 as a potential mediator of the EtOH-induced decrease in muscle protein synthesis.
<>Methods: The effect of acute EtOH intoxication on REDD1 mRNA and protein was determined in striated muscle of rats and mouse myocytes using an RNase protection assay and Western blotting, respectively. Other components of the mTOR signaling pathway were also assessed by immunoblotting. For comparison, REDD1 mRNA/protein was also determined in the muscle of rats chronically fed an alcohol-containing diet for 14 weeks.
<>Results: Intraperitoneal (IP) injection of EtOH increased gastrocnemius REDD1 mRNA in a dose- and time-dependent manner, and these changes were associated with reciprocal decreases in the phosphorylation of 4E-BP1, which is a surrogate marker for mTOR activity and protein synthesis. No change in REDD1 mRNA was detected in the slow-twitch soleus muscle or heart. Acute EtOH produced comparable increases in muscle REDD1 protein. The EtOH-induced increase in gastrocnemius REDD1 was independent of the route of EtOH administration (oral vs. IP), the nutritional state (fed vs. fasted), gender, and age of the rat. The nonmetabolizable alcohol tert-butanol increased REDD1 and the EtOH-induced increase in REDD1 was not prevented by pretreatment with the alcohol dehydrogenase inhibitor 4-methylpyrazole.

<>In contrast, REDD1 mRNA and protein were not increased in the isolated hindlimb perfused with EtOH or in C2C12 myocytes incubated with EtOH, under conditions previously reported to decrease protein synthesis. Pretreatment with the glucocorticoid receptor antagonist RU486 failed to prevent the EtOH-induced increase in REDD1. Finally, the EtOH-induced increase in REDD1 was not associated with altered formation of the TSC1*TSC2 complex or the phosphorylation of TSC2 which is down stream in the REDD1 stress response pathway. In contradistinction to the changes observed with acute EtOH intoxication, REDD1 mRNA/protein was not changed in gastrocnemius from chronic alcohol-fed rats despite the reduction in 4E-BP1 phosphorylation.
<>Conclusions: These data indicate that in fast-twitch skeletal muscle (i) REDD1 mRNA/protein is increased in vivo by acute EtOH intoxication but not in response to chronic alcohol feeding, (ii) elevated REDD1 in response to acute EtOH appears due to the production of an unknown secondary mediator which is not corticosterone, and (iii) the EtOH-induced decrease in protein synthesis can be dissociated from a change in REDD1 suggesting that the induction of this protein is not responsible for the rapid decrease in protein synthesis after acute EtOH administration or for the development of alcoholic myopathy in rats fed an alcohol-containing diet."[324.3.2]

[T] Chronic Alcohol use perturbs tendon healing following injury, making it a bad drug to combine with high load resistance training, or any form of extreme tempo training.

"<>Introduction: Ethanol has a suppressive effect on inflammation and the immune system, but the effect of ethanol on tendon healing in vivo has not been studied. The purpose of this study was to investigate the histological and biomechanical effects of ethanol intake on tendon healing in a rat tendon injury model.
<>Materials and methods: Forty-seven rats were randomly assigned to either ethanol or control groups. Progressively increasing concentrations of ethanol combined with glucose were administered to these rats in their drinking water. After 1 week, the Achilles tendon of each rat was injured proximal to its insertion on the calcaneus. All rats were euthanized at 4 weeks. The tendons were evaluated both histologically and biomechanically. The histologic examination of these tendons was done using a semi-quantitative 4-point scale to rate cell morphology, the degree of ground substance staining, collagen organization, and vascular changes. Load to failure (N) strength was obtained with biomechanical testing.
<>Results: Tendon failure loads were lower in the ethanol group (31.6 +/- 8.8 N) than in the control group (39.7 +/- 8.2 N) (P = 0.04). Histologic tenocyte scores were higher in the ethanol group (1.90 +/- 0.73) than the control group (0.9 +/- 0.73) (P = 0.01).
<>Conclusion: Ethanol ingestion resulted in abnormal tenocyte morphology, disorganized collagen bundles with a tendency toward increased tenocyte number, and neovascularization 3 weeks after the tendon injury indicating delayed and abnormal healing. The healing tendons in the alcohol treated group failed at statistically lower loads than the control group."[324.3.3]

[See: Micro-Essays: The Slow Twitch Athletes Best Friend: Pg. 971]

[See: Lipolytic Supplementation: Hypothermic Alcoholic Browning (HAB)]

My prophylactic supplement list towards combatting chronic alcohol withdrawal-induced myogenic / neurogenic toxicity (CA):

1. CA induces excitotoxicity primarily through the upregulation of the NMDA receptor subunit, NR2B. Agmatine is a selective antagonist of the NR2Br. Agmatine preferentially inhibits the NR2Br's[324.A], thus preventing alcohol withdrawal-induced excitoxicity[324.B].
2. CA induces Aquaporin-4 expression in the brain which correlates with neurotoxicity, DHA counteracts this.[325]
3. CA causes a Thiamine deficiency.[326]
4. CA induces muscle atrophy through TGF-b & Atrogin-1, which can be partially counteracted through increased Cysteine intake or increased Glutathione.[327]
5. CA causes a Carnitine deficiency.[328]
6. CA induces a steep decrease in brain NPY, an anxiolytic chemical. Therefore, Sucralose counteracts one of the deleterious psychological symptoms of CA withdrawal.
   "<>NPY immunoreactivity (NPY-IR) was found in several brain regions, with the hippocampus and cerebral cortex showing the most pronounced changes. NPY-IR was reduced by ethanol treatment in hippocampus and cortex, although at 72 hr of withdrawal there was a dramatic increase in NPY-IR in the hilus of the dentate gyrus and in CA3 and CA2 fields of hippocampus. Ethanol withdrawal seizures occurred around 12 to 24 hr of withdrawal, preceding the changes in NPY-IR at 72 hr. pCREB immunoreactivity (pCREB-IR) tended to decrease during ethanol treatment but showed a dramatic increase in dentate gyrus at 72 hr of withdrawal. Parvalbumin immunoreactivity indicated that some of the pCREB-IR and NPY-IR were within inhibitory interneuron basket cells of the hippocampal hilus. NPY-IR returned to control levels by 168 hr of withdrawal."[329]
7. CA enhances cortisol production, a potent neurotoxin. L-Ornithine would hypothetically prevent this.
   "<>Interactions among the brain, the pituitary gland, and the adrenal glands (i.e., the hypothalamic-pituitary-adrenal [HPA] axis) help regulate the body's response to stress. The adrenal hormone cortisol plays a key role in stress reduction through its effects on multiple body systems. Excessive cortisol activity during both chronic alcohol administration and withdrawal may underlie some of the clinical complications of alcoholism, including increased risk of infectious diseases; bone, muscle, and reproductive system changes; altered energy metabolism; and disorders of mood and intellect. Despite excessive cortisol levels during intoxication and withdrawal, however, the HPA axis becomes less responsive to stress during abstinence, potentially resulting in an impaired capacity to cope with relapse-inducing stressors."[330]

8. CA induces neurotoxic HDAC2 expression, HDAC2 inhibitors such as Valproic Acid or Beta-Hydroxybutyrate would counteract this.[331]

Tetrahydrocannabinol (THC)

The "haze" one experiences under chronic THC influence is facilitated through substantially enhanced neurological COX2 expression by way of G-Protein coupling. Many potheads will attest to feeling a "clarity of thought" or "enhanced performance" when at their "highest", it is not a coincidence COX2 expression associates with memory [See: Important Inflammatory Factors: COX2]. Unfortunately, as with any other inflammatory factor, chronically elevated levels will result in toxicity. The fact that THC shows neurotoxicity through multiple mechanisms beyond COX2 and is stored in fat cells, extending its half-life to nearly unknown timeframes, makes it a very dangerous recreational drug.

Quite interestingly, although the combined use of antioxidants and other anti-inflammatory compounds with THC may protect brain cells to a certain extent from damage, it defeats the purpose of the compound, being that it is the most potent COX2 nootropic.

Here is an interesting piece of a study for consideration before continuing:

"<>It is important to mention that animals exposed to cannabis smoke express an unusual tendency to self-grooming, a complex behavior whose underlying mechanisms cannot be elucidated with a simple visual observation: aberrant self-grooming is indeed a characteristic of neuropsychiatric models, as well as "simple" anxiety or stress signals."[331.1]

[A] THC is addictive, neurotrophic, & neurotoxic through enhancing COX2.

"<>Marijuana has been used for thousands of years as a treatment for medical conditions. However, untoward side effects limit its medical value. Here we show that synaptic and cognitive impairments following repeated exposure to Δ9-tetrahydrocannabinol (Δ9-THC) are associated with the induction of cyclooxygenase-2 (COX-2), an inducible enzyme that converts arachidonic acid to prostanoids, in the brain. COX-2 induction by Δ9-THC is mediated via CB1 receptor-coupled G-protein βγ subunits. Pharmacological or genetic inhibition of COX-2 blocks down-regulation and internalization of glutamate receptor subunits and alterations of the dendritic spine density of hippocampal neurons induced by repeated Δ9-THC exposures. <>Ablation of COX-2 also eliminates Δ9-THC-impaired hippocampal long-term synaptic plasticity, spatial, and fear memories. Importantly, the beneficial effects of decreasing β-amyloid plaques and neurodegeneration by Δ9-THC in Alzheimer's disease animals are retained in the presence of COX-2 inhibition.

<>These results suggest that the applicability of medical marijuana would be broadened by concurrent inhibition of COX-2. >CB1R is coupled to a PTX-sensitive Gi/o protein, and activation of CB1R releases Gβγ subunits from the GTP-bound Gαi subunit. This indicates that COX-2 induction by Δ9-THC is likely mediated through Gβγ."[332]

[B] Acutely administered high dosage THC decreases Error-related Negativity, thereby reducing cognitive flexibility.

"<>Cannabis has been suggested to impair the capacity to recognize discrepancies between expected and executed actions. However, there is a lack of conclusive evidence regarding the acute impact of cannabis on the neural correlates of error monitoring. In order to contribute to the available knowledge, we used a randomized, double-blind, between-groups design to investigate the impact of administration of a low (5.5 mg THC) or high (22 mg THC) dose of vaporized cannabis vs. placebo on the amplitudes of the error-related negativity (ERN) and error positivity (Pe) in the context of the Flanker task, in a group of frequent cannabis users (required to use cannabis minimally 4 times a week, for at least 2 years).
<>Subjects in the high dose group (n=18) demonstrated a significantly diminished ERN in comparison to the placebo condition (n=19), whereas a reduced Pe amplitude was observed in both the high and low dose (n=18) conditions, as compared to placebo. The results suggest that a high dose of cannabis may affect the neural correlates of both the conscious (late), as well as the initial automatic processes involved in error monitoring, while a low dose of cannabis might impact only the conscious (late) processing of errors."[333]

[C] THC reduces social anxiety, revealing the true reason for its popularity among teenagers.

"<>Moreover, activation of CB1 receptors through consumption of THC dampens amygdala reactivity in humans in response to social threat, consistent with the high rate of self-medication and cannabis dependence in individuals with social anxiety. In accordance, it is plausible that deficits in eCB signaling may predispose individuals to social anxiety, and that cannabis use may occur as a means of increasing CB1receptor activation and reducing social anxiety."[334]

[D] THC use may be anabolic through activation of the CB1 receptors in muscle tissue thereby promoting a Fast Twitch fiber program and enhancing satellite cell numbers.

"<>As a principal tissue responsible for insulin-mediated glucose uptake, skeletal muscle is important for whole-body health. The role of peripheral endocannabinoids as regulators of skeletal muscle metabolism has recently gained a lot of interest, as endocannabinoid system disorders could cause peripheral insulin resistance. We investigated the role of the peripheral endocannabinoid system in skeletal muscle development and maintenance. Cultures of C2C12 cells, primary satellite cells and mouse skeletal muscle single fibers

were used as model systems for our studies. We found an increase in cannabinoid receptor type 1 (CB1) mRNA and endocannabinoid synthetic enzyme mRNA skeletal muscle cells during differentiation. We also found that activation of CB1 inhibited myoblast differentiation, expanded the number of satellite cells, and stimulated the fast-muscle oxidative phenotype. Our findings contribute to understanding of the role of the endocannabinoid system in skeletal muscle metabolism and muscle oxygen consumption, and also help to explain the effects of the peripheral endocannabinoid system on whole-body energy balance."[335]

[E] CB1r activation destroys newly formed neurons, although this is likely to be an age dependent or threshold effect.

"<>Activation levels of CB1 receptor directly impacted on actin polymerization and stability via WAVE1 in growth cones of developing neurons, leading to their collapse, as well as in synaptic spines of mature neurons, leading to their retraction."[336]

[F] THC is anxiogenic by way of inhibiting GABA release.

"<>Activation of type 1 cannabinoid receptors (CB1R) decreases GABA and glutamate release in cortical and subcortical regions, with complex outcomes on cortical network activity. To date there have been few attempts to disentangle the region- and cell-specific mechanisms underlying the effects of cannabinoids on cortical network activity in vivo. Here we addressed this issue by combining in vivo electrophysiological recordings with local and systemic pharmacological manipulations in conditional mutant mice lacking CB1R expression in different neuronal populations.
<>First we report that cannabinoids induce hypersynchronous thalamocortical oscillations while decreasing the amplitude of faster cortical oscillations. Then we demonstrate that CB1R at striatonigral synapses (basal ganglia direct pathway) mediate the thalamocortical hypersynchrony, whereas activation of CB1R expressed in cortical glutamatergic neurons decreases cortical synchrony. Finally, we show that activation of CB1 expressed in cortical glutamatergic neurons limits the cannabinoid-induced thalamocortical hypersynchrony. By reporting that CB1R activations in cortical and subcortical regions have contrasting effects on cortical synchrony, our study bridges the gap between cellular and in vivo network effects of cannabinoids. Incidentally, the thalamocortical hypersynchrony we report suggests a potential mechanism to explain the sensory "high" experienced during recreational consumption of marijuana."[337]

[F2] GABA inhibitors are extremely proconvulsant. If you find yourself daydreaming when "high" on THC, you're having a temporal lobe seizure.

"<>GABA in cerebrospinal fluid and brain tissue, and GABA detected during microdialysis studies have been reported in studies of human epileptic brain tissue; GABA agonists suppress seizures, and GABA antagonists produce seizures; Drugs that inhibit GABA synthesis cause seizures; and Benzodiazepines and barbiturates work by

enhancing GABA-mediated inhibition. Finally, drugs that increase synaptic GABA are potent anticonvulsants."[338]

[G] Chronic THC use causes strokes through inhibiting neuronal mitochondrial complexes. A very important study that many will not believe nor heed.

"<>Cannabis has potential therapeutic use but tetrahydrocannabinol (THC), its main psychoactive component, appears as a risk factor for ischemic stroke in young adults. We therefore evaluate the effects of THC on brain mitochondrial function and oxidative stress, key factors involved in stroke. Maximal oxidative capacities V max (complexes I, III, and IV activities), V succ (complexes II, III, and IV activities), V tmpd (complex IV activity), together with mitochondrial coupling (V max/V 0), were determined in control conditions and after exposure to THC in isolated mitochondria extracted from rat brain, using differential centrifugations. Oxidative stress was also assessed through hydrogen peroxide (H2O2) production, measured with Amplex Red. THC significantly decreased V max (−71%; $P < 0.0001$), V succ (−65%; $P < 0.0001$), and V tmpd (−3.5%; $P < 0.001$). <>Mitochondrial coupling (V max/V 0) was also significantly decreased after THC exposure (1.8±0.2 versus 6.3±0.7; $P < 0.001$). Furthermore, THC significantly enhanced H2O2 production by cerebral mitochondria (+171%; $P < 0.05$) and mitochondrial free radical leak was increased from 0.01±0.01 to 0.10±0.01% ($P < 0.001$). Thus, THC increases oxidative stress and induces cerebral mitochondrial dysfunction. This mechanism may be involved in young cannabis users who develop ischemic stroke since THC might increase patient's vulnerability to stroke."[339]

[H] Chronic THC use by way of the CB1 Receptor and TGF-b is a contributing factor in heart disease through causing cardiac fibrosis.

"<>The cannabinoid receptors, CB1 and CB2, are expressed in the heart, but their role under pathological conditions remains controversial. This study examined the effect of CB1 receptor blockade on cardiovascular functions after experimental MI and in experimental metabolic syndrome. MI was induced in Wistar rats by permanent ligation of the left coronary artery. Treatment with the CB1 receptor antagonist rimonabant (10 mg/kg i.p. daily) started 7 days before or 6 h after MI and continued for 6 weeks. Haemodynamic parameters were measured via echocardiography and intracardiac Samba catheter.
<>CB1 blockade improved systolic and diastolic heart function, decreased cardiac collagen and hydroxyproline content and down-regulated TGF-β1. Additionally, rimonabant decreased arterial stiffness, normalised QRS complex duration and reduced brain natriuretic peptide levels in serum. In primary cardiac fibroblasts, rimonabant decreased MMP-9 activity and TGF-β1 expression.
<>Furthermore, rimonabant improved depressed systolic function of spontaneously hypertensive obese rats and reduced weight gain. Blocking of CB1 receptor with rimonabant improves cardiac functions in the early and late stages after MI, decreases arterial stiffness and reduces cardiac remodelling. Rimonabant also has cardioprotective

actions in rats characterised by the metabolic syndrome. Inhibition of proteolysis and TGF-β1 expression and reduced collagen content by rimonabant may attenuate destruction of the extracellular matrix and decrease fibrosis after MI."[340]

[I] Chronic THC tolerance develops after five days, making its concurrent use (for the sake of getting "high"), pointlessly foolish.

"<>We pretreated them for 5 days with 10 mg/kg THC, and then evaluated the effects of vehicle or THC treatment on learning during training in the Morris water maze. We also determined CB1 number and functional coupling in the hippocampus of adolescents and adults.
<>Finally, we measured the time course of hippocampal CB1 desensitization in adolescents and adults during treatment with 10 mg/kg THC or vehicle. Our results indicate that adults, but not adolescents, become tolerant to the effects of THC during water maze training after 5 days of pretreatment."[341]

[J] The true half-life of THC is unknowable as it is stored in fat cells, and therefore it should be used with great caution.

"<>Delta(9)-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis, accumulates in adipose tissue where it is stored for long periods of time. Here we investigated whether conditions that promote lipolysis can liberate THC from adipocytes to yield increased blood levels of THC.
<>The present study shows that lipolysis enhances the release of THC from fat stores back into blood. This suggests the likelihood of 'reintoxication' whereby food deprivation or stress may raise blood THC levels in animals chronically exposed to the drug. Further research will need to confirm whether this can lead to functional effects, such as impaired cognitive function or 'flashbacks'."[342]

[K] Acute THC promotes the release of Pleiotrophin, an obscure cytokine. Whether this is due to a neurological defense mechanism against mitochondrial toxicity, or an unrelated & beneficial effect is as of yet undiscovered.

"<>Delta-9-Tetrahydrocannabinol (THC) is a major psychoactive component of cannabis. We here studied, by quantitative in situ hybridization at the macroscopic level, the possible modulatory effects of acute THC (5 mg/kg/i.p.) on gene expression of the growth factor pleiotrophin (PTN) in the adult rat forebrain. We found, 30 min after a single injection of THC, a significant increase of PTN mRNA concentrations in the cingulate cortex (38%), fronto-parietal cortex (31%) and caudate-putamen (27%). In conclusion, this is the first report on THC regulation of growth factor gene expression in the brain."[343]

[K2] Pleiotrophin plays a role in CNS development and regeneration.

“<>Regeneration in the peripheral nervous system is poor after chronic denervation. Denervated Schwann cells act as a "transient target" by secreting growth factors to promote regeneration of axons but lose this ability with chronic denervation. We discovered that the mRNA for pleiotrophin (PTN) was highly up-regulated in acutely denervated distal sciatic nerves, but high levels of PTN mRNA were not maintained in chronically denervated nerves. PTN protected spinal motor neurons against chronic excitotoxic injury and caused increased outgrowth of motor axons out of the spinal cord explants and formation of "miniventral rootlets."
<>In neonatal mice, PTN protected the facial motor neurons against cell death induced by deprivation from target-derived growth factors. Similarly, PTN significantly enhanced regeneration of myelinated axons across a graft in the transected sciatic nerve of adult rats. Our findings suggest a neurotrophic role for PTN that may lead to previously unrecognized treatment options for motor neuron disease and motor axonal regeneration.“[344]

[K3] Pleiotrophin promotes the release of neurogenic factors after a stroke.
[See: [K?]]

“<>Pleiotrophin (PTN) is an effective neuroprotective factor and its expression is strikingly increased in microglia after ischemia/reperfusion injury. However, whether PTN could provide neurotrophic support to neurons by regulating microglia function is not clear. In this study, we demonstrated that the expression of PTN was induced in microglia after oxygen-glucose deprivation/reperfusion. PTN promoted the proliferation of microglia by enhancing the G1 to S phase transition. PTN also stimulated the secretion of brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF) and nerve growth factor (NGF) in microglia, but did not upregulate the expression of proinflammatory factors such as TNF-α, IL-1β and iNOS.
<>Mechanistically, we found that PTN increased the phosphorylation of extracellular signal-regulated kinase (ERK) 1/2 in microglia in both concentration-dependent and time-dependent manners. In addition, ERK1/2 inhibitor U0126 abolished the proliferation and G1 to S phase transition of microglia stimulated by PTN, and inhibited the production of BDNF, CNTF and NGF induced by PTN. In conclusion, our results demonstrated that PTN-ERK1/2 pathway plays important role in regulating microglia growth and secretion of neurotrophic factors. These findings provide new insight into the neuroprotective role of PTN and suggest that PTN is a new target for therapeutic intervention of stroke.”[345]

[L] Caffeine prevents THC-induced COX2 expression through inhibiting the activity of the G-Protein receptor. To combine the two drugs defeats the purpose of *high* dose THC.

“<>Chronic administration of caffeine in mice (intraperitoneally, 3 mg/kg/day, for 15 days, >12 h before trials) led to an A1-mediated enhancement of the CB1-dependent acute disruptive effects of THC on a short-term spatial memory task, despite inducing a

reduction in cortical and hippocampal CB1 receptor number and an attenuation of CB1 coupling with G protein."[346]

[M] THC inhibits the formation of Amyloids through GSK-3B.

"<>The purpose of this study was to investigate the potential therapeutic qualities of Δ9-tetrahydrocannabinol (THC) with respect to slowing or halting the hallmark characteristics of Alzheimer's disease. N2a-variant amyloid-β protein precursor (AβPP) cells were incubated with THC and assayed for amyloid-β (Aβ) levels at the 6-, 24-, and 48-hour time marks. THC was also tested for synergy with caffeine, in respect to the reduction of the Aβ level in N2a/AβPPswe cells. THC was also tested to determine if multiple treatments were beneficial. The MTT assay was performed to test the toxicity of THC. Thioflavin T assays and western blots were performed to test the direct anti-Aβ aggregation significance of THC. Lastly, THC was tested to determine its effects on glycogen synthase kinase-3β (GSK-3β) and related signaling pathways.
<>From the results, we have discovered THC to be effective at lowering Aβ levels in N2a/AβPPswe cells at extremely low concentrations in a dose-dependent manner. However, no additive effect was found by combining caffeine and THC together. We did discover that THC directly interacts with Aβ peptide, thereby inhibiting aggregation. Furthermore, THC was effective at lowering both total GSK-3β levels and phosphorylated GSK-3β in a dose-dependent manner at low concentrations. At the treatment concentrations, no toxicity was observed and the CB1 receptor was not significantly upregulated. Additionally, low doses of THC can enhance mitochondria function and does not inhibit melatonin's enhancement of mitochondria function. These sets of data strongly suggest that THC could be a potential therapeutic treatment option for Alzheimer's disease through multiple functions and pathways."[347]

[N] Ultra-Low Dose THC is a neuroprotectant by activating CREB & ERK1/2. 0.002mg x kg is the dosage listed below, and that equates to a dosage under a milligram of THC for the average adult. For a clearer idea, 0.002mg x 70kg Bodyweight = 0.14mg = 140mcg, and 1mg THC = 1000mcg. Most Cannabis flowers contain over 100mg of THC once cured, and an average "hit" of Cannabis smoke or vapor is above 20mg of THC. Remember this dosage lasted for "7-Weeks". I do not suggest using CBD Oils to microdose THC and they are best not combined; you instead should find big brand THC gummies or products that can be segmented into dosages easily.

"<>We have previously reported that a single injection of an ultra-low dose of delta-9-tetrahydrocannabinol (THC; the psychoactive ingredient of marijuana) protected the brain from pentylenentetrazole (PTZ)-induced cognitive deficits when applied 1-7 days before or 1-3 days after the insult. In the present study we expanded the protective profile of THC by showing that it protected mice from cognitive deficits that were induced by a variety of other neuronal insults, including pentobarbital-induced deep anesthesia, repeated treatment with 3,4 methylenedioxymethamphetamine (MDMA; "ecstasy") and exposure to carbon monoxide.

<>The protective effect of THC lasted for at least 7 weeks. The same ultra-low dose of THC (0.002 mg/kg, a dose that is 3-4 orders of magnitude lower than the doses that produce the known acute effects of the drug in mice) induced long-lasting (7 weeks) modifications of extracellular signal-regulated kinase (ERK) activity in the hippocampus, frontal cortex and cerebellum of the mice. The alterations in ERK activity paralleled changes in its activating enzyme MEK and its inactivating enzyme MKP-1. Furthermore, a single treatment with the low dose of THC elevated the level of pCREB (phosphorylated cAMP response element-binding protein) in the hippocampus and the level of BDNF (brain-derived neurotrophic factor) in the frontal cortex. These long-lasting effects indicate that a single treatment with an ultra-low dose of THC can modify brain plasticity and induce long-term behavioral and developmental effects in the brain."[348]

[O] THC in a dosage of 1mg / kg or 3mg / kg of bodyweight reverses memory decline in *aged* mice, whereas CBD does not, due to the necessity of activated CB1 receptors. Clearly THC is a recreational chemical best used by older individuals, whereas CBD has more benefits for the young.

"<>Decline in cognitive performance, an aspect of the normal aging process, is influenced by the endocannabinoid system (ECS). Cannabinoid receptor 1 (CB1) signaling diminishes with advancing age in specific brain regions that regulate learning and memory and abolishing CB1 receptor signaling accelerates cognitive aging in mice. We recently demonstrated that prolonged exposure to low dose (3 mg/kg/day) Δ9-tetrahydrocannabinol (THC) improved the cognitive performances in old mice on par with young untreated mice.
<>Here we investigated the potential influence of cannabidiol (CBD) on this THC effect, because preclinical and clinical studies indicate that the combination of THC and CBD often exhibits an enhanced therapeutic effect compared to THC alone. We first tested the effectiveness of a lower dose (1 mg/kg/day) THC, and then the efficacy of the combination of THC and CBD in 1:1 ratio, same as in the clinically approved medicine Sativex®.
<>Our findings reveal that a 1 mg/kg/day THC dose still effectively improved spatial learning in aged mice. However, a 1:1 combination of THC and CBD failed to do so. The presence of CBD induced temporal changes in THC metabolism ensuing in a transient elevation of blood THC levels. However, as CBD metabolizes, the inhibitory effect on THC metabolism was alleviated, causing a rapid clearance of THC.
<>Thus, the beneficial effects of THC seemed to wane off more swiftly in the presence of CBD, due to these metabolic effects. The findings indicate that THC-treatment alone is more efficient to improve spatial learning in aged mice than the 1:1 combination of THC and CBD."[348.1]

[P] Early Marijuana users tend to have enhanced brain connectivity in the Orbitofrontal Cortex and Forceps Minor, at the cost of brain shrinkage (similar to chronic obesity), clearly explained by the same "neurotoxic compensatory mechanism" whereby chronic

alcohol use enhances neuronal connectivity, at the cost of behavioral flexibility. This increase in functional connectivity (FA) decreases after around year eight of use. A lower Orbitofrontal Cortex volume associates with depression[349.A], and obesity (overeating)[349.B]. While decreased functional connectivity in the Forceps minor is associated with a increase in age associated cognitive decline[349.C]

"<>Questions surrounding the effects of chronic marijuana use on brain structure continue to increase. To date, however, the findings remain inconclusive. In this comprehensive study that aimed to characterize brain alterations associated with chronic marijuana use, we measured gray matter (GM) volume via structural MRI across the whole brain by using voxel-based morphology, synchrony among abnormal GM regions during resting state via functional connectivity MRI, and white matter integrity (i.e., structural connectivity) between the abnormal GM regions via diffusion tensor imaging in 48 marijuana users and 62 age- and sex-matched nonusing controls.
<>The results showed that compared with controls, marijuana users had significantly less bilateral orbitofrontal gyri volume, higher functional connectivity in the orbitofrontal cortex (OFC) network, and higher structural connectivity in tracts that innervate the OFC (forceps minor) as measured by fractional anisotropy (FA). Increased OFC functional connectivity in marijuana users was associated with earlier age of onset. Lastly, a quadratic trend was observed suggesting that the FA of the forceps minor tract initially increased following regular marijuana use but decreased with protracted regular use. This pattern may indicate differential effects of initial and chronic marijuana use that may reflect complex neuroadaptive processes in response to marijuana use. Despite the observed age of onset effects, longitudinal studies are needed to determine causality of these effects."
"<>To determine the potential downstream effects of OFC volume reduction, we evaluated OFC functional (fcMRI) and structural connectivity (DTI). Functional connectivity analysis revealed greater connectivity within the OFC network in marijuana users compared with controls, which is concordant with existing resting-state studies and task-based studies. This increased functional connectivity in users may suggest a compensatory mechanism whereby greater network recruitment is engaged to compensate for OFC liability. Tomasi et al. illustrated how greater functional connectivity requires higher glucose consumption (~70% of brain's energy consumption), and, consequently, hubs of higher functional connectivity must be efficient.
<>In their report, the OFC was described as having high glucose efficiency as measured by the ratio between the strength of functional integration (based on rsfMRI and the number of connections of the network nodes) and cerebral metabolic rate of glucose. Taken together, because the OFC is a network hub, observed increase in OFC functional connectivity concomitant with reductions in OFC gray matter may suggest neuroadaptive plasticity."
"<>The findings of greater functional connectivity in OFC network in marijuana users were echoed by increased structural connectivity (i.e., FA) of the forceps minor in marijuana users relative to controls. Greater FA has been suggested to reflect better

myelination and/or intact axons. Based on RD and AD measurements, it appears that the FA difference between the groups in the forceps minor was driven by lower RD, suggesting greater myelination in the marijuana users."[349]

[Q] Cannabidiol increases the concentration of THC in the brain, thereby hypothetically magnifying the deleterious effects that THC exerts on the brain once the CBD breaks down in the body. To clarify, it is logical to suggest that when THC is present in the brain in low concentrations, and CBD is also present in low or high concentrations, the net effect is neuroprotection, but THC has an extremely long and unknowable half-life owing to its fat solubility, meaning that it is unlikely CBD will remain elevated in the body during frequent THC use, and owning to CB1 receptor desensitization, escalating dosages of THC will be used, leading to accelerating neurotoxicity, that of which may be magnified if this unhealthily high concentration of THC is further increased through CBD use.

"<>Methods: Adolescent rats were treated with ascending daily THC doses over 21 days (1 then 3 then 10 mg/kg). Some rats were given equivalent CBD doses 20 min prior to each THC injection to allow examination of possible antagonistic effects of CBD. During dosing, rats were assessed for THC and CBD/THC effects on anxiety-like behaviour, social interaction and place conditioning. At the end of dosing, blood and brain levels of THC, and CB(1) and 5-HT(1A) receptor binding were assessed.
<>Results: CBD potentiated an inhibition of body weight gain caused by chronic THC, and mildly augmented the anxiogenic effects, locomotor suppressant effects and decreased social interaction seen with THC. A trend towards place preference was observed in adolescent rats given CBD/THC but not those given THC alone. With both acute and chronic administration, CBD pre-treatment potentiated blood and brain THC levels, and lowered levels of THC metabolites (THC-COOH and 11-OH-THC). CBD co-administration did not alter the THC-induced decreases in CB(1) receptor binding and no drug effects on 5-HT(1A) receptor binding were observed."[349.0]

Mitochondrial Complex Toxicity & Psychosis Prophylaxis:

[1] Docosahexaenoic Acid is a potent treatment option for stroke-induced brain damage. [See: Anti-Inflammation Cycle Dietary Fats: DHA / EPA]

"<>Mitophagy, the selective removal of damaged mitochondria through autophagy, is crucial for mitochondrial turnover and quality control. Docosahexaenoic acid (DHA), an essential omega-3 fatty acid, protects mitochondria in various diseases. This study aimed to investigate the neuroprotective role of DHA in ischaemic stroke models in vitro and in vivo and its involvement in mitophagy and mitochondrial dysfunction. A mouse model of ischaemic stroke was established through middle cerebral artery occlusion (MCAO). To simulate ischaemic stroke in vitro, PC12 cells were subjected to oxygen–glucose deprivation (OGD). Immunofluorescence analysis, western blotting (WB), electron

microscopy (EM), functional behavioural tests, and Seahorse assay were used for analysis.
<>DHA treatment significantly alleviated the brain infarction volume, neuronal apoptosis, and behavioural dysfunction in mice with ischaemic stroke. In addition, DHA enhanced mitophagy by significantly increasing the number of autophagosomes and LC3-positive mitochondria in neurons. The Seahorse assay revealed that DHA increased glutamate and succinate metabolism in neurons after ischaemic stroke. JC-1 and MitoSox staining, and evaluation of ATP levels indicated that DHA-induced mitophagy alleviated reactive oxygen species (ROS) accumulation and mitochondrial injury.
<>Mechanistically, DHA improved mitochondrial dynamics by increasing the expression of dynamin-related protein 1 (Drp1), LC3, and the mitophagy clearance protein Pink1/Parkin. Mdivi-1, a specific mitophagy inhibitor, abrogated the neuroprotective effects of DHA, indicating that DHA protected neurons by enhancing mitophagy. Therefore, DHA can protect against neuronal apoptosis after stroke by clearing the damaged mitochondria through Pink1/Parkin-mediated mitophagy and by alleviating mitochondrial dysfunction."[349.01]

[2] Creatine protects mitochondria, may enhance exercise-induced mitochondrial biogenesis, and activates the GABAA receptors.
[See: Anti-Inflammation Cycle Supplementation]

"<>The current study focused on the effect of creatine supplementation with/without exercise on the expression of genes controlling mitochondrial biogenesis in skeletal and cardiac muscles, as well as its safety profile on the liver and kidney.
<>A total of 40 male Wister rats were included in the present study. Two unexercised groups: The control sedentary group and the sedentary creatine-treated group (n=10) were treated daily with oral creatine (0.5 g/kg per day). Two exercised groups performed swimming exercise training 5 days/week for a period of 5 weeks; The Exercise training group, and exercise training and creatine (0.5 g/kg per day) treated group. After sacrifice, blood samples, cardiac and soleus muscles were collected for assessment of mtDNA copy number, gene expression analysis and nuclear extraction for the assay of PGC-1α.
<>The results of the current study demonstrated that, physical activity with short-term creatine supplementation increased all factors of mitochondrial biogenesis, an effect that is devoid of any kidney or liver adverse effects. Further studies are still required to explore the potential of creatine supplementation in ameliorating mitochondrial diseases, including epilepsy, skeletal and cardiac myopathies, hepatopathies and nephropathies."[349.1]

[3] EGCg enhances mitochondrial biogenesis in neurons.
[See: Anti-Inflammation Cycle Supplementation]

"<>A critical role for mitochondrial dysfunction has been proposed in the pathogenesis of Down's syndrome (DS), a human multifactorial disorder caused by trisomy of chromosome 21, associated with mental retardation and early neurodegeneration.

Previous studies from our group demonstrated in DS cells a decreased capacity of the mitochondrial ATP production system and overproduction of reactive oxygen species (ROS) in mitochondria. In this study we have tested the potential of epigallocatechin-3-gallate (EGCG) - a natural polyphenol component of green tea - to counteract the mitochondrial energy deficit found in DS cells. We found that EGCG, incubated with cultured lymphoblasts and fibroblasts from DS subjects, rescued mitochondrial complex I and ATP synthase catalytic activities, restored oxidative phosphorylation efficiency and counteracted oxidative stress. These effects were associated with EGCG-induced promotion of PKA activity, related to increased cellular levels of cAMP and PKA-dependent phosphorylation of the NDUFS4 subunit of complex I.
<>In addition, EGCG strongly promoted mitochondrial biogenesis in DS cells, as associated with increase in Sirt1-dependent PGC-1α deacetylation, NRF-1 and T-FAM protein levels and mitochondrial DNA content. In conclusion, this study shows that EGCG is a promoting effector of oxidative phosphorylation and mitochondrial biogenesis in DS cells, acting through modulation of the cAMP/PKA- and sirtuin-dependent pathways. EGCG treatment promises thus to be a therapeutic approach to counteract mitochondrial energy deficit and oxidative stress in DS."[352]

[4] L-Theanine (in adolescent brains, and possibly adult brains), counteracts the neurological abnormalities that result from THC use[1], and this effect is likely, at least partially, through inhibition of the CB1 Receptor[2], making it not only neuroprotective against THC use, but also a way to combat CB1r desensitization in those who enjoy its acutely administered disorientating psychological effects.

[4.1] "<>l-Theanine is a characteristic amino acid in tea with various effects including antioxidant and anti-inflammatory effects. Previously, most studies had reported that l-theanine regulates the immune function in vivo by inhibiting the expression of the inflammatory factors, but how l-theanine regulates the inflammatory factors' pathway is not known.
<>In this study, we innovatively found the binding target of l-theanine in vivo-cannabinoid receptor 1, and demonstrated that l-theanine regulated the immune function and glutamine metabolism by competitively binding cannabinoid receptor 1. Mechanistically, l-theanine competitively binds cannabinoid receptor 1, leading to inhibition of cannabinoid receptor 1 activity, and regulates glutamine metabolism and immune function in normal and E44813-stressed rats. In normal rats, l-theanine inhibits ERK1/2 phosphorylation through Gβγ by antagonizing cannabinoid receptor 1, thus affecting GS expression.
<>From the point of view of immune signaling, after LTA antagonizes the activity of cannabinoid receptor 1, it relieves the inhibition of cannabinoid receptor 1 on COX-2 expression, downregulates Pdcd4 expression and NFκB, and ultimately enhances the expression of the anti-inflammatory factor IL-10. In E44813-stressed rats, l-theanine promotes the nuclear translocation of p-ERK1/2 by inhibiting the activity of cannabinoid receptor 1, and finally acts on GS. At the same time, it decreases the expression of the

pro-inflammatory factor TNF-α and increases the expression of the anti-inflammatory factor IL-10 in stressed rats through the COX2-Pdcd4-NFκB-IL10 and TNFα pathways.
<>In summary, these results demonstrate that l-theanine regulates glutamine metabolism and immune function by competitively binding to cannabinoid receptor 1." [352.1]

[4.2] "<>Chronic adolescent exposure to Δ-9-tetrahydrocannabinol (THC) is linked to elevated neuropsychiatric risk and induces neuronal, molecular and behavioral abnormalities resembling neuropsychiatric endophenotypes. Previous evidence has revealed that the mesocorticolimbic circuitry, including the prefrontal cortex (PFC) and mesolimbic dopamine (DA) pathway are particularly susceptible to THC-induced pathologic alterations, including dysregulation of DAergic activity states, loss of PFC GABAergic inhibitory control and affective and cognitive abnormalities.
<>There are currently limited pharmacological intervention strategies capable of preventing THC-induced neuropathological adaptations. l-Theanine is an amino acid analog of l-glutamate and l-glutamine derived from various plant sources, including green tea leaves. l-Theanine has previously been shown to modulate levels of GABA, DA, and glutamate in various neural regions and to possess neuroprotective properties.
<>Using a preclinical model of adolescent THC exposure in male rats, we report that l-theanine pretreatment before adolescent THC exposure is capable of preventing long-term, THC-induced dysregulation of both PFC and VTA DAergic activity states, a neuroprotective effect that persists into adulthood.
<>In addition, pretreatment with l-theanine blocked THC-induced downregulation of local GSK-3 (glycogen synthase kinase 3) and Akt signaling pathways directly in the PFC, two biomarkers previously associated with cannabis-related psychiatric risk and subcortical DAergic dysregulation. Finally, l-theanine powerfully blocked the development of both affective and cognitive abnormalities commonly associated with adolescent THC exposure, further demonstrating functional and long-term neuroprotective effects of l-theanine in the mesocorticolimbic system."[352.2]

Capsaicin

Capsaicin is a very interesting chemical, unconsciously craved by day laborers and physically exhausted men throughout generations, for good reason, as it promotes muscle hypertrophy and enhances endurance, at the cost of it being a gastrointestinal irritant. From personal experience, Capsaicin causes tendonitis after four weeks of chronic use, due to its anti-fibrotic properties, although it is still a supplement to consider, especially if you go on vacation (detraining) and seek to mitigate the absorption of high carb or high fat meals and wish to protect your muscles against atrophy.

You may wonder how much Capsaicin is required to reach the muscles during dietary consumption, and I will say from subjective experience that one ghost pepper consumed will result in noticeable, if short lived, TRPV1 receptor activation within the muscles.

[A] Capsaicin delays regeneration of motor nerves but accelerates muscle regeneration, making it a bad supplement for high intensity (explosive: high load) exercise athletes, but one with negligible effects for low intensity (endurance: low load) exercise athletes.

"<>Trauma or the tourniquet used in orthopedic surgery is often associated with ischemia-reperfusion (I/R) injury with a consequent decrease of muscle power. To explore whether components of the neuromuscular junction (NMJ) are involved in this muscle dysfunction, NMJs were ultrastructurally characterized in the extensor digitorum longus muscle of rats at reperfusion times of 1, 24, 72, and 168 h after a 120-min arterial occlusion. Disorganization of the presynaptic membrane and mitochondrial injury was noted at 1 h, followed by fragmentation and partial engulfment of nerve terminals by Schwann cells at 24 and 72 h. The magnitude of degenerative changes declined at 168 h, suggesting the commencement of regeneration. The postsynaptic membrane remained intact throughout the whole period.
<>In our previous study, deafferentation with pretreatment of the sciatic nerve with capsaicin, which reduces neurogenic inflammation and has a selective effect on nociceptive fibers, improved functional recovery of the muscle after I/R. The present results document a significantly delayed structural regeneration of the motor nerve terminals after combined capsaicin and I/R treatment. Since capsaicin treatment alone had no discernible effect on the structure of NMJs, the findings point to a possibly indirect effect of capsaicin on the motor nerves, which may predispose them to increased susceptibility unmasked only by a subsequent injury. The mismatch between the enhanced functional improvement of the muscle and delayed regeneration of the nerve after capsaicin pretreatment questions the efficient use of such deafferentation to protect the integrity of neuromuscular junctions in I/R injury."[353]

[B] Capsaicin mimics mechanical load to activate myogenic factors and stimulate hypertrophy through promoting Calcium Ion release by way of the TRPV1 receptors.

"<>Mechanical load-induced intracellular signaling events are important for subsequent skeletal muscle hypertrophy. We previously showed that load-induced activation of the cation channel TRPV1 caused an increase in intracellular calcium concentrations ([Ca2+]i) and that this activated mammalian target of rapamycin (mTOR) and promoted muscle hypertrophy.
<>However, the link between mechanical load-induced intracellular signaling events, and the TRPV1-mediated increases in [Ca2+]i are not fully understood. Here we show that administration of the TRPV1 agonist, capsaicin, induces phosphorylation of mTOR, p70S6K, S6, Erk1/2 and p38 MAPK, but not Akt, AMPK or GSK3β (to stimulate hypertrophy). Furthermore, the TRPV1-induced phosphorylation patterns resembled those induced by mechanical load. Our results continue to highlight the importance of TRPV1-mediated calcium signaling in load-induced intracellular signaling pathways.
<>Our study suggests the activation of TRPV1-mediated increase in [Ca2+] to be an important step in the induction of hypertrophy."[354]

[C] Capsaicin is anti-fibrotic 1: Through inhibition of TGF-b.

"<>Capsaicin (CPS) exerts many pharmacological effects, but any possible influence on liver fibrosis remains unclear. Therefore, we evaluated the inhibitory effects of CPS on dimethylnitrosamine (DMN) and TGF-β1-induced liver fibrosis in rats and hepatic stellate cells (HSCs). CPS inhibited DMN-induced hepatotoxicity, NF-κB activation, and collagen accumulation. CPS also suppressed the DMN-induced increases in α-SMA, collagen type I, MMP-2, and TNF-α. In addition, CPS inhibited DMN-induced TGF-β1 expression (from 2.3 ± 0.1 to 1.0 ± 0.1) and Smad2/3 phosphorylation (from 1.5 ± 0.1 to 1.1 ± 0.1 and from 1.6 ± 0.1 to 1.1 ± 0.1, respectively) by activating Smad7 expression (from 0.1 ± 0.0 to 0.9 ± 0.1) via PPAR-γ induction (from 0.2 ± 0.0 to 0.8 ± 0.0) ($p < 0.05$). Furthermore, in HSCs, CPS inhibited the TGF-β1-induced increases in α-SMA and collagen type I expression, via PPAR-γ activation. These results indicate that CPS can ameliorate hepatic fibrosis by inhibiting the TGF-β1/Smad pathway via PPAR-γ activation."[355]

[C2] Capsaicin is anti-fibrotic 2.

"<>Capsaicin is a versatile plant product which has been ascribed several health benefits and anti-inflammatory and analgesic properties. We have investigated the effect of capsaicin on the molecular stability, self-assembly, and fibril stability of type-I collagen. It was found that capsaicin suppresses collagen fibril formation, increases the stability of collagen fibers in tendons, and has no effect on the molecular stability of collagen. Turbidity assay data show that capsaicin does not promote disassembly of collagen fibrils. However, capsaicin moderately protects collagen fibrils from enzymatic degradation. Computational studies revealed the functions of the aromatic group and amide region of capsaicin in the collagen-capsaicin interaction. The results may have significant implications for capsaicin-based therapeutics that target excess collagen accumulation-linked pathology, for example thrombosis, fibrosis, and sclerosis."[356]

[D] Capsaicin promotes lipolysis through UCP-2.

"Capsaicin (8-methyl-N-vanillyl-6-nonenamide) is a pungent ingredient of red peppers, and has been reported to reduce body weight gain and adiposity in rodents. The present study investigated the effects of capsaicin on lipid catabolism in differentiated 3T3-L1 adipocytes. Capsaicin decreased the intracellular lipid content in a concentration-dependent manner. The release of glycerol into the medium was increased by the addition of capsaicin. The mRNA levels of genes involved in lipid catabolism such as hormone sensitive lipase (HSL), carnitine palmitoyl transferase-Iα (CPTI-α) and uncoupling protein 2 (UCP2) were up-regulated significantly. These results suggest that capsaicin exerts its lipolytic action by increasing the hydrolysis of triacylglycerol in adipocytes, and that these effects are mediated at least partially by regulation of the expression of multiple genes that are involved in the lipid catabolic pathway, such as HSL and CPT-Iα, and those involved in thermogenesis such as UCP2."[357]

[E] Capsaicin enhances muscular endurance and strength.

“<>Chili pepper is used as a food, seasoning and has been revered for its medicinal and health claims. It is very popular and is the most common spice worldwide. Capsaicin (CAP) is a major pungent and bioactive phytochemical in chili peppers. CAP has been shown to improve mitochondrial biogenesis and adenosine triphosphate (ATP) production. However, there is limited evidence around the effects of CAP on physical fatigue and exercise performance. The purpose of this study was to evaluate the potential beneficial effects of CAP on anti-fatigue and ergogenic functions following physiological challenge. Female Institute of Cancer Research (ICR) mice from four groups (n = 8 per group) were orally administered CAP for 4 weeks at 0, 205, 410, and 1025 mg/kg/day, which were respectively designated the vehicle, CAP-1X, CAP-2X, and CAP-5X groups. The anti-fatigue activity and exercise performance was evaluated using forelimb grip strength, exhaustive swimming time, and levels of serum lactate, ammonia, glucose, BUN (blood urea nitrogen) and creatine kinase (CK) after a 15-min swimming exercise. <>The grip strength and exhaustive swimming time of the CAP-5X group were significantly higher than other groups. CAP supplementation dose-dependently reduced serum lactate, ammonia, BUN and CK levels, and increased glucose concentration after the 15-min swimming test. In addition, CAP also increased hepatic glycogen content, an important energy source for exercise. The possible mechanism was relevant to energy homeostasis and the physiological modulations by CAP supplementation. Therefore, our results suggest that CAP supplementation may have a wide spectrum of bioactivities for promoting health, performance improvement and fatigue amelioration.”[358]

[F] Capsaicin is a gastrointestinal irritant.

"<>Chilli (containing the active ingredient capsaicin) forms an important flavouring agent in the preparation of meals in the tropics. Previous studies have shown that capsaicin in high doses causes gross structural and functional changes in the gut. The present study investigates the effect of pure capsaicin on the absorption of glucose, water and alanine by the small intestine of the rat. Perfusion studies were carried out using a 10 cm jejunal segment. Absorption rates of glucose, water and alanine from a control solution containing the nutrient and from a test solution containing added capsaicin were compared. Recovery of absorptive function of the intestinal mucosa after exposure to capsaicin was also studied. Absorption of water, glucose and alanine was found to be significantly reduced in the presence of capsaicin. Recovery of absorptive function occurred when capsaicin was withdrawn from the perfusate. It was concluded that capsaicin adversely affected absorption of nutrients from the rat small intestine; this effect was reversible at least in the case of some nutrients."[359]

[G] Capsaicin is lipolytic through enhancing butyrate-producing bacteria and through inhibiting the CB1 Receptor.

"<>Metabolic endotoxemia originating from dysbiotic gut microbiota has been identified as a primary mediator for triggering the chronic low-grade inflammation (CLGI) responsible for the development of obesity. Capsaicin (CAP) is the major pungent bioactivator in chili peppers and has potent anti-obesity functions, yet the mechanisms linking this effect to gut microbiota remain obscure. Here we show that mice fed a high-fat diet (HFD) supplemented with CAP exhibit lower levels of metabolic endotoxemia and CLGI associated with lower body weight gain. High-resolution responses of the microbiota were examined by 16S rRNA sequencing, short-chain fatty acid (SCFA) measurements, and phylogenetic reconstruction of unobserved states (PICRUSt) analysis. <>The results showed, among others, that dietary CAP induced increased levels of butyrate-producing Ruminococcaceae and Lachnospiraceae, while it caused lower levels of members of the lipopolysaccharide (LPS)-producing family S24_7. Predicted function analysis (PICRUSt) showed depletion of genes involved in bacterial LPS synthesis in response to CAP. We further identified that inhibition of cannabinoid receptor type 1 (CB1) by CAP also contributes to prevention of HFD-induced gut barrier dysfunction. Importantly, fecal microbiota transplantation experiments conducted in germfree mice demonstrated that dietary CAP-induced protection against HFD-induced obesity is transferrable. Moreover, microbiota depletion by a cocktail of antibiotics was sufficient to block the CAP-induced protective phenotype against obesity, further suggesting the role of microbiota in this context. Together, our findings uncover an interaction between dietary CAP and gut microbiota as a novel mechanism for the anti-obesity effect of CAP acting through prevention of microbial dysbiosis, gut barrier dysfunction, and chronic low-grade inflammation.
<>IMPORTANCE: Metabolic endotoxemia due to gut microbial dysbiosis is a major contributor to the pathogenesis of chronic low-grade inflammation (CLGI), which primarily mediates the development of obesity. A dietary strategy to reduce endotoxemia appears to be an effective approach for addressing the issue of obesity. Capsaicin (CAP) is the major pungent component in red chili (genus Capsicum). Little is known about the role of gut microbiota in the anti-obesity effect of CAP. High-throughput 16S rRNA gene sequencing revealed that CAP significantly increased butyragenic bacteria and decreased LPS-producing bacteria (e.g., members of the S24-7 family) and LPS biosynthesis. By using antibiotics and microbiota transplantation, we prove that gut microbiota plays a causal role in dietary CAP-induced protective phenotype against high-fat-diet-induced CLGI and obesity. Moreover, CB1 inhibition was partially involved in the beneficial effect of CAP. Together, these data suggest that the gut microbiome is a critical factor for the anti-obesity effects of CAP."[360]

[H] Capsaicin promotes IGF-1 release in the brain, thereby promoting memory processes. Although this study suggests that capsaicin induces angiogenesis, that is in contradiction to many others, which display its potent anti-angiogenic effects, although it is possible this pro-angiogenesis effect is organ specific, such that its effects on brain versus muscle differ.

"<>Calcitonin gene-related peptide (CGRP) increases the production of insulin-like growth factor-I (IGF-I) in the mouse brain. IGF-I exerts beneficial effects on the cognitive function by increasing synaptic transmission and by inducing angiogenesis and neurogenesis in the hippocampus. In the current study, we examined whether stimulation of sensory neurons by capsaicin improved the cognitive function by increasing the production of IGF-I in the hippocampus using wild-type (WT) and CGRP-knockout (CGRP-/-) mice. Significant increases of the hippocampal tissue levels of CGRP, IGF-I, and IGF-I messenger RNA (mRNA) were observed after capsaicin administration in WT mice ($P < 0.01$) but not in CGRP-/- mice. Increase in the expression of c-fos was also observed in the spinal dorsal horn, the parabrachial nuclei, and the hippocampus after capsaicin administration in WT mice but not in CGRP-/- mice.
<>Significant enhancement of angiogenesis and neurogenesis was observed in the dentate gyrus of the hippocampus after capsaicin administration in WT mice ($P < 0.01$) but not in CGRP-/- mice. Although capsaicin administration improved spatial learning in WT mice, no such effect was observed in CGRP-/- mice. Capsaicin-induced improvement of the spatial learning was reversed by administration of an anti-IGF-I antibody and by that of a CGRP receptor antagonist CGRP (8-37) in WT mice. The administration of IGF-I improved the spatial learning in both WT and CGRP-/- mice. These observations strongly suggest that the stimulation of sensory neurons by capsaicin might increase IGF-I production via increasing the hippocampal tissue CGRP levels, and it may thereby promote angiogenesis and neurogenesis to produce improvement of the cognitive function in mice."[360.1]

[See: Anti-Inflammation Cycle Supplementation: Caffeine]

[See: Pro-Inflammation Cycle Supplementation: Nicotine]

Natural & Artificial Sweeteners

The best sweetener for drinks or food is the amino acid Glycine, which has a subtle sweet flavor, promotes myogenesis, aids in the biochemical repair of tendons, & promotes sleep, whereas Serine possesses a sweetness that may not be as pleasurable to most people's palate, but is equally as anabolic. Any chemical that tastes sweet, regardless if it is swallowed or not, will elicit insulin release, this is called cephalic phase insulin release, and that includes Glycine and Serine, remember that if you're on the strictest lipolytic diet.

Monk Fruit

[A] The Monk Fruit chemical components, Mogrosides, may promote DNA repair through PARP1 & TRP53, proteins that associate with aging. Mogrosides appear to be very potent anti-inflammatory chemicals, and should be used sparingly.

"<>Inflammatory properties of mogrosides in both murine macrophage RAW 264.7 cells and a murine ear edema model. The results indicate that mogrosides can inhibit inflammation induced by lipopolysaccharides (LPS) in RAW 264.7 cells by down-regulating the expression of key inflammatory genes iNOS, COX-2, and IL-6 and up-regulating some inflammation protective genes such as PARP1, BCL2l1, TRP53, and MAPK9. Similarly, in the murine ear edema model, 12-O-tetradecanoylphorbol-13-acetate-induced inflammation was inhibited by mogrosides by down-regulating COX-2 and IL-6 and up-regulating PARP1, BCL2l1, TRP53, MAPK9, and PPARδ gene expression."[362]

[B] Morgroside V promotes neurite outgrowth in response to an NMDA receptor antagonist.

"<>Here, we investigated its protective effects against neuronal damages elicited by MK-801 treatment. Our behavioral experimental results showed that MK-801-induced PPI deficits and social withdrawal were prevented by MogV treatment. Moreover, the cellular and neurochemical responses of MK-801 in medial prefrontal cortical cortex (mPFC) were also ameliorated by MogV treatment.
<>Also, profiling metabolites assay through artificial intestinal microbiota was performed to identify bioactive components of MogV. An in vitro study of primary neuronal culture demonstrated that MogV and its metabolite 11-oxo-mogrol treatment prevented the MK-801-induced neuronal damages through the mechanisms of promoting neurite outgrowth, inhibiting cell apoptosis, and [Ca2+]i release. <>Additionally, 11-oxo-mogrol reversed inactivation of phosphorylation levels of AKT and mTOR induced by MK801."[363]

[C] Monk Fruit enhances physical performance, but it does not burn fat, because like all sweeteners, natural or not, it promotes insulin release.

"<>In this study, the effects of Siraitia grosvenorii fruits extracts (SGFE) on physical fatigue were investigated. One hundred and forty-four mice were randomly divided into four groups: control group, low-dose SGE-treated group, middle-dose SGE-treated group and high-dose SGFE-treated group. The animals of control group received an oral administration of physiological saline in a volume of 2.5 mL, and the animals of treated group received the same volume of SGFE (100, 200 and 400 mg/Kg bodyweight, once a day) for 28 days.
<>After 28 days, anti-fatigue effects of SGFE were assessed 10 h after the last treatment by forced swimming test and some biochemical parameters related to fatigue, including blood lactic acid, serum urea nitrogen, liver glycogen and muscle glycogen were measured. The data showed that SGFE can extend the swimming time of the mice, as well as increasing the liver and muscle glycogen contents, but decrease the blood lactic acid and serum urea nitrogen levels. These results indicated that Siraitia grosvenorii fruits extracts had significant anti-fatigue effects on mice and these effects were dose-dependent."

<>It was found (data not shown) that the body weights of mice in the SGFE-treated groups (LT, MT and HT group) were not different significantly from that in the control group (C group) at day 0 or 28 ($p > 0.05$), which means the SGFE has no effect on body weight."[364]

[D] As expected, Monk fruit extract will stimulate insulin release.

"<>Luo han kuo fruit (Siraitia grosvenori Swingle), a fruit native to China, has been used as a natural sweetening agent for centuries and has been reported to be beneficial for diabetic population. However, limited research has been conducted to elucidate the relationship between the sweetening action and biological parameters that may be related to potential health benefits of LHK fruit (Luo Han Kuo fruit). The present study examined the effect of LHK fruit and its chemical components on insulin secretion using an in vitro cell model system. Mogroside V is the most abundant and the sweetest chemical component among the mogrosides in LHK fruit.
<>The experimental data demonstrated that the crude LHK extract stimulated the secretion of insulin in pancreatic beta cells; furthermore, pure mogroside V isolated from LHK fruit also exhibited a significant activity in stimulating insulin secretion by the beta cells, which could partially be responsible for the insulin secretion activity of LHK fruit and fruit extract.
<>The current study supports that LHK fruit/extract has the potential to be natural sweetener with a low glycemic index, and that mogroside V, possible other related mogrosides, can provide a positive health impact on stimulating insulin secretion."[365]

Sucralose

This is the most insidious of all toxins, found in nearly every flavored protein powder, and sugar free drink (2025), it suppresses the immune system, enhances intestinal Ecoli growth, and promotes adipogenesis by two distinct mechanisms (appetite / insulin), although it is a nootropic, while being capable of causing damage to the brainstem. Because Sucralose increases NPY and AMPK in the brain, it is capable of promoting memory processes, and appears to have some synergy with caffeine, but chronic use is surely a mistake due to the risk of developing obesity or dysbiosis.

[A] Sucralose enhances appetite through promoting Neuropeptide Y.
"<>Non-nutritive sweeteners like sucralose are consumed by billions of people. While animal and human studies have demonstrated a link between synthetic sweetener consumption and metabolic dysregulation, the mechanisms responsible remain unknown.
<>Here we use a diet supplemented with sucralose to investigate the long-term effects of sweet/energy imbalance. In flies, chronic sweet/energy imbalance promoted hyperactivity, insomnia, glucose intolerance, enhanced sweet taste perception, and a sustained increase in food and calories consumed, effects that are reversed upon sucralose removal.

<>Mechanistically, this response was mapped to the ancient insulin, catecholamine, and NPF/NPY systems and the energy sensor AMPK, which together comprise a novel neuronal starvation response pathway. Interestingly, chronic sweet/energy imbalance promoted increased food intake in mammals as well, and this also occurs through an Neuropeptide-Y-dependent mechanism. Together, our data show that chronic consumption of a sweet/energy imbalanced diet triggers a conserved neuronal fasting response and increases the motivation to eat."[366]

[A2] Neuropeptide Y promotes memory.

"<>Neuropeptide Y (NPY) and its receptors (especially Y1, Y2, and Y5) are highly expressed in brain regions involved in learning and memory processes. Accordingly, NPY was shown to modulate cognitive functions in rodents. Here, we investigated possible memory-enhancing effects of NPY and determined the role of the NPY system in the acquisition, consolidation, and retrieval of non-social and social memory in mice, using the object and social discrimination tests, respectively. Intracerebroventricular (icv) infusion of NPY (1 nmol/2 µl) prolonged retention of non-social (object) memory, but not of social memory. This effect was blocked by the Y1 receptor antagonist BIBO3304 trifluoroacetate (2 nmol/2 µl), but not by the Y2 receptor antagonist BIIE0246 (2 nmol/2 µl).
<>While icv infusion of NPY did not affect the acquisition, consolidation, and retrieval of non-social and social memory, icv infusion of BIBO3304 trifluoroacetate and BIIE0246 blocked the consolidation of non-social memory and the retrieval of both non-social and social memory. This study suggests that NPY has memory-enhancing effects in a non-social context by specifically acting on Y1 receptors. It further suggests that the central NPY system exerts differential effects on the sequential phases of non-social and social memory."[367]

[A3] Sucralose likely promotes memory through NPY. Mice administered Sucralose during cognitive testing show performance that exceeds the control, as well as Aspartame and Stevia groups, and this is related to less neuronal damage occurring in the Sucralose mice compared to the previous groups. Sucralose may therefore be a good chemical nootropic when paired with caffeine, at the cost of a healthy intestinal microbiome. Interestingly, in severely high dosages, Sucralose damages the brainstem.

"<>Sucralose is a hydrolyzed product of 6-chloro-6-deoxyglucose that enters the brain through the blood by inhibiting the process of d-glucose transportation across the epithelium. It was also found that it competes with the glucose uptake in the brain and causes d-glucose concentration to drop and chlorinated sugar to rise. Since the neurons cannot store glucose, they depend on the concentration of glucose in the blood stream to function properly. However, this group showed the fastest rate among all groups in locating the platform, as their test for memory. In addition to this, the chemical component of sucralose which is 6-chloro-6-deoxyglucose, was found to cause lesion in

the nuclei of brainstem, cerebellum and spinal cord which is the most probable reason why there's a minimal percentage of cellular apoptosis found in the hippocampus."[368]

[B] Sucralose is a contributing factor in intestinal infections.

"<>Because of heavy use of antimicrobials, antimicrobial resistance in bacteria has become of great concern. The effect of some widely used food additives such as sucralose on bacteria in the gut and the environment has also drawn increasing attention. In this study, we investigated the interaction between antimicrobials and sucralose impacting antimicrobial resistance and mutation of Escherichia coli (E. coli). <>To examine antimicrobial resistance and mutation frequency, different subinhibitory concentrations of sucralose were added to cultures of E.coli BW25113 that were then treated with antimicrobials, oxolinic acid, or moxifloxacin. Then the E.coli were assayed for bacterial survival and recovery of mutants resistant to an unrelated antimicrobial, rifampicin. Pre-treatment of E.coli BW25113 with 1/2 minimal inhibitory concentration (MIC) of sucralose increased the survival rate in oxolinic acid or moxifloxacin. A 1/3 MIC of sucralose increased rifampicin-resistant mutation rate of E.coli BW25113 after 72 h, while rifampicin-resistant mutation rate was increased when co-treated with 1/8 MIC, 1/4 MIC, 1/3 MIC sucralose, and oxolinic acid after 24 h. Sucralose can increase the antimicrobial resistance and mutation frequency of E.coli to some antimicrobials."[369]

[C] Sucralose is an immunosuppressant.

"<>Exposure of blood cells to sucralose-containing sweeteners under stimulatory conditions reduced levels of the biomarker of humoral immunity, Interleukin-10 ($P < 0.001$). The cumulative suppression of Interleukin-6 and Interleukin-10 levels induced by sucralose may contribute to the inability in mounting an effective humoral response when posed with an exogenous threat."[370]

[D] Sucralose increases Insulin release.

"<>Compared to Wk0, consumption of sucralose for 10 weeks provoked 1) increased insulin concentrations. These data show that chronic consumption of sucralose can affect insulin and glucose responses in non-insulin resistant healthy young adults with normal body mass index."[371]

Stevia

[A] Stevia causes dopaminergic dysfunction by destroying beneficial intestinal flora.

"<>In conclusion, we found that RebA consumption impacted gene expression in the mesolimbic reward center and certain cecal microbial taxa while prebiotic consumption altered body composition, food intake, glucose tolerance, and cecal microbiota community structure. Additionally, RebA increased SCFAs acetate and valerate, which

were positively correlated with fat mass and total weight. Consuming prebiotic alongside RebA tended to mitigate stevia-driven alterations in the mesolimbic reward circuitry and microbiota but attenuated the increase in cecum weight associated with prebiotic intake. Since we observed that RebA reduced the relative abundance of certain "health-promoting" gut microbiota, future studies should examine weight and metabolic outcomes following RebA consumption in populations that exhibit dysbiotic gut microbial compositions (i.e., obese, diabetic)."[372]

[B] Stevia is Anti-Fibrotic.

"<>We found for the first time that stevia cotreatment prevented the elevation of serum markers of necrosis and cholestasis and the occurrence of liver fibrosis. It is worth noting that stevia downregulated several profibrogenic pathways, including the reduction of hepatic myofibroblasts and decreased matrix metalloproteinase (MMP)2 and MMP13 expression, thereby blocking the liberation of transforming growth factor-β from the extracellular matrix. Notably, stevia reduced the phosphorylation of pSmad3L, the most profibrogenic and mitogenic Smad, by inhibiting the activation of c-Jun N-terminal kinase and extracellular signal-regulated kinase. Interestingly, Smad7, an important antifibrotic molecule, was upregulated by stevia treatment in cirrhotic rats. These multitarget mechanisms led to the prevention of experimental cirrhosis."[373]

[C] Stevia reduces insulin release[1] by activating GLUT4 (Glucose transporter type 4) by way of Akt[2], similarly to insulin.

[1] "<>Consumption of stevia in preloads significantly lowered postprandial insulin levels compared to both aspartame and sucrose."[374]

[2] "<>Likewise the insulin effect, steviol glycosides caused an increase in glucose uptake into rat fibroblasts by activating the PI3K/Akt pathway, thus inducing Glut4 translocation to the plasma membrane. The presence of S961, an insulin antagonist, completely abolished these effects, allowing to hypothesize that steviol glycosides could act as ligands of the same receptor engaged by insulin."[375]

Sorbitol

[A] Sorbitol promotes Lactobacillus growth.

"<>A potential prebiotic action has been ascribed to sorbitol, but in vivo evidence of this remains scarce. In the present work, the effect of sorbitol was compared to that of fructo-oligosaccharides (FOS) in a rat model. Microbiota changes, particularly in lactobacilli, were analyzed on fecal, colonic and cecal samples. Denaturing gradient gel electrophoresis (DGGE) analysis of 16S rRNA gene amplicons using universal primers showed that FOS and sorbitol diets exerted a strong influence upon gut microbiota

patterns. When Lactobacillus group-specific primers were used, DGGE profiles revealed five DNA bands that belonged to Lactobacillus johnsonii, Lactobacillus sp. AD102, Lactobacillus intestinalis, Lactobacillus murinus and Lactobacillus reuteri. <>Although these species are present in all dietary groups, quantification by real-time PCR showed that sorbitol and FOS intake increased L. reuteri cell numbers, and sorbitol also contributed to maintaining the levels of Lactobacillus sp. AD102. Analysis of organic acid concentrations showed that sorbitol intake significantly increased colonic and cecal butyrate levels. Hence, sorbitol, which is widely used as a low-calorie sweetener, has the capacity, in our animal model, to modify gut microbiota activity in such a way as to possibly contribute to healthy colonic mucosa."[375.1]

[B] Sorbitol and by association all Sugar Alcohols reduce the absorption of other factors transiting through the intestines through drawing water into the intestines, making them strong laxatives.

"<>Objective: To quantify small bowel digestion and absorption of sorbitol, isomalt and maltitol in ileostomy patients and estimate the metabolizable energy. Subjects: Study A: Nine ileostomy patients, under a constant controlled diet, ate during three consecutive days 2 milk chocolate bars per day, containing 2 x 15 g of polyol, each day with another polyol in random order. The first bar was taken 30 min after breakfast, and the second bar, 7 h after breakfast. Effluents were recovered during the whole study. Study B: 5, 10 or 20 g of sorbitol or isomalt were consumed each day in a drink during two 3-day periods by two ileostomy subjects. The recovery in the ileal effluent was measured over 24 h.
<>Results: Study A: Carbohydrate recovery in ileostomy effluent was 26.8 +/- 2.8% (mean+SEM) for sorbitol, 24.8 + 5.7% for maltitol (2/3 as sorbitol) and 40.0 +/- 0.7% for isomalt (1/3 being sorbitol and mannitol). Ileal excretion, compared with a day without polyol, was compared in 4 subjects. The total volume excreted, as well as dry matter increased after polyol consumption. When taking this extra loss into account, the metabolizable energy value of the polyols for 2 x 15 g intake were: sorbitol, 12 kJ/g (2.8 kcal/g); maltitol, 13 kJ/g (3.1 kcal/g); isomalt, 9 kJ/g (2.1 kcal/g). Study B: The level of digestion and absorption of both sugar alcohols was dose dependent. <>Conclusions: These results indicate that sorbitol, maltitol and isomalt are rather extensively absorbed, but the digestibility of the other nutrients is also reduced, due to the osmotic load caused by the polyols in the small intestine. There are evidences of a dose dependency of the energy value of the polyols."[375.2]

Erythritol

[A] Erythritol scavenges Hydrogen radicals, making it an antioxidant.

"<>We studied the antioxidant properties of erythritol in vitro and subsequently determined its antioxidant activity and its vasoprotective effect in the streptozotocin diabetic rat. Results: Erythritol was shown to be an excellent HO* radical scavenger and an inhibitor of 2,2'-azobis-2-amidinopropane dihydrochloride-induced hemolysis but inert toward superoxide radicals. High-performance liquid chromatographic and electron spin resonance spectroscopy studies showed that the reaction of erythritol with hydroxyl radicals resulted in the formation of erythrose and erythrulose by abstraction of a carbon-bound hydrogen atom. In the streptozotocin diabetic rat, erythritol displayed an endothelium-protective effect and, in accordance with the in vitro experiments, erythrose was found in the urine of erythritol-consuming rats."[376]

[A2] Hydroxyl Radicals are associated with muscle atrophy, most predominately during aging.

“<>Male Wistar rats (15 weeks old), the ankle joints of one hindlimb of which were immobilized in the extended position for 12 days, were injected with salicylate as a trapping agent for hydroxyl radicals before sacrifice. Atrophied and contralateral soleus, typical slow red muscles were collected and their levels of 2,3-dihydroxybenzoic acid (2,3-DHB), one of the main reaction products formed by the attack of hydroxyl radical on salicylate, were determined using high-performance liquid chromatography with an electrochemical detector. There was a significant increase in 2,3-DHB in the atrophied muscle. This result strongly suggests the enhanced generation in vivo of hydroxyl radicals in atrophied muscle.”[377]

[B] Erythritol is positively associated with adipogenesis.

"<>Metabolomic markers associated with incident central adiposity gain were investigated in young adults. In a 9-mo prospective study of university freshmen (n = 264). Blood samples and anthropometry measurements were collected in the first 3 d on campus and at the end of the year. Plasma from individuals was pooled by phenotype [incident central adiposity, stable adiposity, baseline hemoglobin A1c (HbA1c) > 5.05%, HbA1c < 4.92%] and assayed using GC-MS, chromatograms were analyzed using MetaboliteDetector software, and normalized metabolite levels were compared using Welch's t test.
<>Assays were repeated using freshly prepared pools, and statistically significant metabolites were quantified in a targeted GC-MS approach. Isotope tracer studies were performed to determine if the potential marker was an endogenous human metabolite in men and in whole blood. Participants with incident central adiposity gain had statistically significantly higher blood erythritol [$P < 0.001$, false discovery rate (FDR) = 0.0435], and the targeted assay revealed 15-fold [95% confidence interval (CI): 13.27, 16.25] higher blood erythritol compared with participants with stable adiposity. Participants with baseline HbA1c > 5.05% had 21-fold (95% CI: 19.84, 21.41) higher blood erythritol compared with participants with lower HbA1c ($P < 0.001$, FDR = 0.00016).

<>Erythritol was shown to be synthesized endogenously from glucose via the pentose-phosphate pathway (PPP) in stable isotope-assisted ex vivo blood incubation experiments and through in vivo conversion of erythritol to erythronate in stable isotope-assisted dried blood spot experiments. Therefore, endogenous production of erythritol from glucose may contribute to the association between erythritol and obesity observed in young adults."[378]

[C] Erythritol magnifies brain damage by inhibiting Angiogenesis. This study displays the primary downside of antioxidant compounds that suppress angiogenesis.

"<>After long-term treatment with fructose, erythritol (sugar alcohols), acesulfame K (artificial sweeteners), or rebaudioside A (rare sugars), the cerebral ischemic injury (both infarct volumes and neurobehavioral outcomes) was significantly aggravated, angiogenesis in ischemic brain was reduced, and endothelial progenitor cell function was impaired in mice compared with control. However, the similar impairments were not found in sucrose (with the same dose as fructose's)-treated mice.
<>Conclusions: Long-term consumption of sugar substitutes aggravated cerebral ischemic injury in mice, which might be partly attributed to the impairment of endothelial progenitor cells and the reduction of angiogenesis in ischemic brain. This result implies that dietary intake of sugar substitutes warrants further attention in daily life."[379]

Mannose

Mannose positively associates with a lean phenotype (body makeup) when administered early in life but has limited-zero positive effects in adulthood. Give to the child & withhold from the adult?

"<>Mannose is an important monosaccharide for protein glycosylation in mammals but is an inefficient cellular energy source. Using a C57BL6/J mouse model of diet-induced obesity, we show that mannose supplementation of high-fat-diet-fed mice prevents weight gain, lowers adiposity, reduces liver steatosis, increases endurance and maximal O2 consumption, and improves glucose tolerance. Mannose-supplemented mice have higher fecal energy content, suggesting reduced caloric absorption by the host.
<>Mannose increases the Bacteroidetes to Firmicutes ratio in the gut microbiota, a signature associated with the lean phenotype. These beneficial effects of mannose are observed when supplementation is started early in life. Functional transcriptomic analysis of cecal microbiota revealed profound and coherent changes in microbial energy metabolism induced by mannose that are predicted to lead to reduced energy harvest from complex carbohydrates by gut microbiota. Our results suggest that the gut microbiota contributes to mannose-induced resistance to deleterious effects of a high-fat diet."
<>We next assessed the utility of mannose treatment as an intervention after onset of diet-induced obesity (DIO). We weaned 16 mice on HFD. 8 mice were supplemented with 2% mannose at 8 weeks PW. Mice gained weight (42.9 ± 1.4 g; 19 weeks) and fat

mass (13.5 ± 0.9 g) on HFD as expected. Surprisingly, mannose neither reduced weight (43.1 ± 0.8 g; 19 weeks) or fat mass (13.6 ± 0.8 g), implying that mannose-mediated protection from DIO is lost unless mannose is provided early in life. This, coupled with the fact that continuous mannose supplementation is required, suggests that mannose exerts its effects via a factor that can be modulated early in life and persists only as long as mannose is provided."[379.1]

!!CAUTION!! Xylitol !!CAUTION!!

Another insidious sweetener that is found in far too many protein bars, far worse than Sucralose, that promotes Oxalate formation in the body.

"<>Identification of crystals deposited in brain and kidney after xylitol administration by biochemical, histochemical, and electron diffraction methods"[380]

!!CAUTION!! Aspartame !!CAUTION!!

My favorite sweetener, flavor-wise, happens to be angiogenic at the cost of extreme neurotoxicity and cancer development. Jay Cutler leading up to one his Olympia performances said that he would drink "3-Gallons of Sugar-Free Tang per day", which contains high concentrations of Aspartame.[380.1]

[A] Aspartame is angiogenic.

"<>Angiogenesis is the process of generating new blood vessels from preexisting vessels and is considered essential in many pathological conditions. The purpose of the present study is to evaluate the effect of aspartame on angiogenesis in vivo chick chorioallantoic membrane (CAM) and wound-healing models as well as in vitro 2,3-bis-2H-tetrazolium-5-carboxanilide (XTT) and tube formation assays. In CAM assay, aspartame increased angiogenesis in a concentration-dependent manner. Compared with the control group, aspartame has significantly increased vessel proliferation ($p < 0.001$).
<>In addition, in vivo rat model of skin wound-healing study showed that aspartame group had better healing than control group, and this was statistically significant at $p < 0.05$. There was a slight proliferative effect of aspartame on human umbilical vein endothelial cells on XTT assay in vitro, but it was not statistically significant; and there was no antiangiogenic effect of aspartame on tube formation assay in vitro. <>These results provide evidence that aspartame induces angiogenesis in vitro and in vivo; so regular use may have undesirable effect on susceptible cases."[381]

[B] Aspartame is highly cytotoxic.

"<>Additionally, significant increment of acetylcholine esterase activity concomitant with the reduction of antioxidant molecules (SOD, CAT, GSH-Px and GSH), and

induction of malondialdehyde level are precisely indicative of oxidative brain damage. Brain mRNA transcripts of target genes showed that aspartame and soft drink induced upregulation of BAX, Casp3, P27 and Mdm2 (1.5-fold) and down-regulation of Bcl2, suggesting an activation of cellular apoptosis.
<>Collectively, subchronic aspartame and soft drink-induced brain damage in rats may be driven via a mechanism that involves energy production disruption, electrolytes and hormonal imbalance, increased oxidative stress and activation of molecular pathway of neuronal apoptosis."[382]

Probiotics, Fibers, & Short Chain Fatty Acids

Intestinal florae are now understood to play a significant role in neurological & immunological function, from altering neurotransmitter concentrations in the brain, to reducing or increasing systemic inflammation. This is called the Gut-Brain Axis.

The bacteria within our intestines consume fiber, sugar, and other carbohydrate molecules passing through our gastrointestinal tract resulting in the excretion (fermentation) of Short Chain Fatty Acids: Acetate, Butyrate, & Propionic Acid, as well as the promotion of cell division (growth) of microbiota. The Short Chain Fatty Acids (SCFA's) are absorbed into the GI tract and exert systemic effects. The primary downside of consuming fibers is the resulting enhanced dietary cholesterol absorption.

Regarding Probiotics supplements, although many are proprietary and do not list the exact concentrations of organisms, and numerous probiotics contained within do not survive extended shelf life, there is no reason not to experiment. One may also buy live and active cultures and ferment them to create their own living foods and drinks.

Nearly all Lactobacillaceae (Lactobacillus) strains and Bifidobacteriaceae (Bifidobacterium) strains will benefit your mind and body, consider starting your probiotic journey with these families of bacteria. Sauerkrauts, cottage cheeses, and yogurts are some of the least expensive, easily accessible, and possibly most beneficial probiotic food products available to us.
To my current understanding, most beneficial probiotics are Anti-Inflammatory, except for one that of which promotes a safe form of Inflammation [See: Pro-Inflammation Supplementation].

Some fibers are immunostimulatory through stimulating an immune reaction when they come in contact during later digestion with a part of our intestines called the **Peyer's Patches**. The body assumes these molecules are pathogenic bacteria, and thus a systemic immune reaction is stimulated. Arabinogalactans & Beta-Glucans are thought to activate the Peyer's patches.

All Fibers and most prebiotics are carbohydrates, primarily Polysaccharides or Monosaccharides. Carbohydrates makeup the plant walls, or "the bodies" of plants. Consuming healthy fibers is not adequate treatment for microbiome dysfunction, only probiotic supplementation will yield an effective outcome at an unfortunate great monetary cost.

Inflammatory intestinal bacteria primarily promote lipolysis through enhancing the expression of systemic inflammatory factors, and by producing acetic acid (vinegar) after digesting intestinal ruffage. Inflammation aside, the supplementation of vinegar should be considered an essential part of any weight loss protocol.

Interestingly, certain research articles that I disagree with heavily have asserted that gut lactobacilli count positively associate with obesity. This may be partially true, in that as we have learned, anti-inflammatory processes in the body reduce lipolytic metabolism, but it cannot be completely true, for when unhealthy intestinal florae grow in number, insulin resistance invariably occurs, and when physiological sickness develops, exercise protocols are often abandoned invariably leading to expedited death.

It is strange how great a role our microbiome plays in our memory, mood, & musculature, and we may never fully understand the intricacies that our intestinal flora & skin flora played in our evolution, alongside retroviruses from space, & Volatile Organic Compounds. We can, however, take better care of the symbiotic brothers and sisters who reside within our bodies by better moderating how we eat, and what we drink, for the question presents itself, does a person with dysbiosis crave junk food because their unhealthy bacteria crave junk food i.e. do bacteria in our intestines exert some sort of highly specific digestive-neurogenic-craving signaling in our brains?

Finally, stomach acid is a major barrier towards Probiotic absorption, and it is an unanswered question of mine as of now if decreasing stomach acid would enhance their absorption and passage into the lower digestive tract, but it may be a worthy idea to test.

[See: The Tetrad of Human Experience: Psychological Stress Addendum 1: The Microbiome]

[See: Anti-Inflammation Cycle Supplementation: Vegetable Juicing: Ginger Root]

[A] Intestinal florae, through interacting with neurotransmitter levels, hormones, and inflammatory factors, either increases or reduces stress resilience.

"<>Exposure to traumatic stress is a major risk factor for development of neuropsychiatric disorders in a sub-population of individuals, while others remain resilient. The mechanisms and contributing factors differentiating between these phenotypes are still unclear. We hypothesize that inter-individual differences in the microbial composition and function contribute to host resilience or susceptibility to stress-induced psychopathologies.
<>The current study aimed to characterize gut microbial community before and after exposure to traumatic stress in an animal model of PTSD. Sprague-Dawley male rats were randomly divided into unstressed controls and experimental group subjected to Single Prolonged Stress (SPS). After 14 days, behavioral analyses were performed using Open Field, Social Interaction and Elevated Plus Maze tests. Based on the anxiety measures, the SPS group was further subdivided into resilient (SPS-R) and susceptible (SPS-S) cohorts. The animals were sacrificed after the last behavioral test and cecum, colon, hippocampus, and medial prefrontal cortex were dissected. Prior to SPS and

immediately after Open Field test, fecal samples were collected from each rat for 16S V3-V4 ribosomal DNA sequencing, whereas urine samples were collected before SPS, 90 min into immobilization and on the day of sacrifice to measure epinephrine and norepinephrine levels.
<>Analyses of the fecal microbiota revealed significant differences in microbial communities and in their predictive functionality among the groups before and after SPS stressors. Before SPS, the SPS-S subgroup harbored microbiota with an overall pro-inflammatory phenotype, whereas SPS-R subgroup had microbiota with an overall anti-inflammatory phenotype, with predictive functional pathways enriched in carbohydrate and lipid metabolism and decreased in amino acid metabolism and neurodegenerative diseases. After SPS, the gut microbial communities and their predictive functionality shifted especially in SPS cohorts, with volatility at the genus level correlating inversely with Anxiety Index. In line with the alterations seen in the gut microbiota, the levels of cecal short chain fatty acids were also altered, with SPS-S subgroup having significantly lower levels of acetate, valerate and caproate. The levels of acetate inversely correlated with Anxiety Index.
<>Interestingly, urinary epinephrine and norepinephrine levels were also higher in the SPS-S subgroup at baseline and during stress, indicative of an altered sympathoadrenal stress axis. Finally, shorter colon (marker of intestinal inflammation) and a lower claudin-5 protein expression (marker for increased blood brain barrier permeability) were observed in the SPS-S subgroup. Taken together, our results suggest microbiota is a potential factor in predisposing subjects either to stress susceptibility or resilience. Moreover, SPS triggered significant shifts in the gut microbiota, their metabolites and brain permeability. These findings could lead to new therapeutic directions for PTSD possibly through the controlled manipulation of gut microbiota. It may enable early identification of individuals more likely to develop prolonged anxiogenic symptoms following traumatic stress."[382.1]

[B] Intestinal Flora are able to change the concentrations of neurotransmitters in the brain through releasing neurotransmitters in the gut and interacting with the "Second Brain", which is the Enteric Nervous System (ENS) i.e. the nervous system of the intestines that contains hundreds of millions of neurons.

"<>We recently coined the phrase 'psychobiotics' to describe an emerging class of probiotics of relevance to psychiatry. Such "mind-altering" probiotics may act via their ability to produce various biologically active compounds, such as peptides and mediators normally associated with mammalian neurotransmission. Several molecules with neuroactive functions such as gamma-aminobutyric acid (GABA), serotonin, catecholamines and acetylcholine have been reported to be microbially-derived, many of which have been isolated from bacteria within the human gut. Secreted neurotransmitters from bacteria in the intestinal lumen may induce epithelial cells to release molecules that in turn modulate neural signalling within the enteric nervous system and consequently signal brain function and behaviour of the host. <>Consequently, neurochemical containing/producing probiotic bacteria may be viewed as delivery vehicles for

neuroactive compounds and as such, probiotic bacteria may possibly have the potential as a therapeutic strategy in the prevention and/or treatment of certain neurological and neurophysiological conditions."[382.2]

[C] The Enteric Nervous System, being composed of millions of neurons, is capable of similar memory processes such as Long-Term Potentiation.

"<>John Furness and colleagues went further to ask which neurons remain hyperexcitable after the conditional stimulus and may thereby act as the "memory storage". In the ENS, a rather low frequency (1 Hz) of electrical stimulation of interganglionic fiber tracts for 4–30 min induces a sustained slow postsynaptic excitation (SSPE)."
"<>The ENS shows electrophysiological properties reminiscent of long-term potentiation in the brain (LTP). SSPE in sensory networks may be responsible for memorizing altered sensitivity of neurons to a stimulus to adapt to different digestive needs or to evoke responses under pathological conditions."[382.3]

[D] The probiotic Lactobacillus Rhamnosus activates the Vagus Nerve, a cranial nerve that innervates (connects to) numerous parts of the body, such as the intestines. When activated, the Vagus Nerve exerts an anxiolytic effect through interaction with GABA receptors[1] and is capable of promoting LTP[2]. [See: The Nervous System]

[1] "<>There is increasing, but largely indirect, evidence pointing to an effect of commensal gut microbiota on the central nervous system (CNS). However, it is unknown whether lactic acid bacteria such as Lactobacillus rhamnosus could have a direct effect on neurotransmitter receptors in the CNS in normal, healthy animals. GABA is the main CNS inhibitory neurotransmitter and is significantly involved in regulating many physiological and psychological processes. Alterations in central GABA receptor expression are implicated in the pathogenesis of anxiety and depression, which are highly comorbid with functional bowel disorders.
<>In this work, we show that chronic treatment with L. rhamnosus (JB-1) induced region-dependent alterations in GABA(B1b) mRNA in the brain with increases in cortical regions (cingulate and prelimbic) and concomitant reductions in expression in the hippocampus, amygdala, and locus coeruleus, in comparison with control-fed mice.
<>In addition, L. rhamnosus (JB-1) reduced GABA(Aα2) mRNA expression in the prefrontal cortex and amygdala, but increased GABA(Aα2) in the hippocampus. Importantly, L. rhamnosus (JB-1) reduced stress-induced corticosterone and anxiety- and depression-related behavior. Moreover, the neurochemical and behavioral effects were not found in vagotomized mice, identifying the vagus as a major modulatory constitutive communication pathway between the bacteria exposed to the gut and the brain.
<>Together, these findings highlight the important role of bacteria in the bidirectional communication of the gut-brain axis and suggest that certain organisms may prove to be useful therapeutic adjuncts in stress-related disorders such as anxiety and depression."[382.4]

[2] "<>Previous studies have demonstrated that electrical stimulation of the vagus nerve (VNS) delivered at a moderate intensity following a learning experience enhances memory in laboratory rats and human subjects, while VNS at lower or higher intensities has little or no effect. This finding suggests that VNS may affect memory processes by modulating neural plasticity in brain structures associated with memory storage such as the hippocampus.
<>To test this hypothesis, the present study investigated the modulatory effect of VNS on the development of long-term potentiation (LTP) in the dentate gyrus of freely-moving rats. Rats receiving 0.4 mA VNS showed enhanced potentiation of the population spike amplitude for at least 24 h after tetanus relative to the sham-stimulation group. In contrast, no such effect was observed with 0.2 mA VNS. Stimulation at 0.8 mA had a short-term effect and tended to enhance early LTP, but to a lesser extent than did 0.4 mA. The 0.4 mA stimulation was the same intensity that was previously shown to enhance retention performance in an inhibitory avoidance task.
<>These findings suggest that the neural mechanisms underlying the mnemonic effect of VNS may involve modulating synaptic plasticity in the hippocampus. These data also suggest that neural activity in the vagus nerve, occurring as a result of changes in peripheral state, is an important mechanism by which emotional experiences and arousal can enhance the storage of memories of those experiences."[382.5]

[C] Beta-Glucan stimulates the Peyer's patches.

"<>One possible mechanism for the uptake of β-glucan in the lumen could be passage through microfold cells (M cells) in the Peyer's patches of the small intestinal lumen. The luminal surface of the intestine limits the access of pathogens and antigens to underlying host tissues, and is protected by a single layer of epithelial cells bound by tight junctions. Located within the follicle-associated epithelium (FAE) of Peyer's patches, and occasionally within the villus epithelia, are M cells, a unique subset of specialized epithelial cells for transepithelial transport of macromolecules and particulate antigens"[383]

[C2] Arabinogalactan stimulates the Peyer's patches, although unlike Beta-Glucan, it is a gastrointestinal irritant.

"<>Udani hypothesizes that arabinogalactan is capable of stimulating the Peyer's patches in the gut as it traverses the intestines. The larch polysaccharides may have a similar structure to these potentially pathogenic bacteria, and therefore, provide a low level of stimulation, which keeps an array of antibodies ready in case the actual antigen appears."[384]

[D] Sugar enhances the absorption of Probiotics.

"<>Lactobacillus rhamnosus GG is an industrially significant probiotic strain with proven health benefits. In this study, the effect of glucose on L. rhamnosus GG survival

was analyzed in simulated gastric juice at pH 2.0. It was found that the presence of 19.4 mM glucose resulted in up to 6-log10-enhanced survival following 90 min of exposure. Further work with dilute HCl confirmed that glucose was the sole component responsible. Comparative analysis with other Lactobacillus strains revealed that enhanced survival was apparent in all strains, but at different pH values. The presence of glucose at concentrations from 1 to 19.4 mM enhanced L. rhamnosus GG survival from 6.4 to 8 log10 CFU ml(-1) in simulated gastric juice.
<>The mechanisms behind the protective effect of glucose were investigated. Addition of N',N'-dicyclohexylcarbodiimide to simulated gastric juice caused survival to collapse, which was indicative of a prominent role in inhibition of F0F1-ATPase. Further work with neomycin-resistant mutants that exhibited 38% to 48% of the F0F1-ATPase activity of the parent confirmed this, as the survival in the presence of glucose of these mutants decreased 3 x 10(6)-fold compared with the survival of the wild type (which had a viability of 8.02 log10 CFU ml(-1)).
<>L. rhamnosus GG survival in acidic conditions occurred only in the presence of sugars that it could metabolize efficiently. To confirm the involvement of glycolysis in the glucose effect, iodoacetic acid was used to inhibit glyceraldehyde-3-phosphate dehydrogenase (GAPDH) activity. The reduction in GAPDH activity caused survival to decrease by 8.30 log10 CFU ml(-1) in the presence of glucose. The data indicate that glucose provides ATP to F0F1-ATPase via glycolysis, enabling proton exclusion and thereby enhancing survival during gastric transit."[385]

Probiotics

Amazake / Shio Koji

It's clear that our microbiome plays a role in the cellular aging of our bodies, and our brains, but there is one bacterium, Blautia Coccoides, that appears to be associated with lifespan in Japanese adults. B. Coccoides was found to be abundant in individuals with a decreased abundance of Bacteroides, making it an Anti-Aging bacterium. Koji is a rice or soybean that has been inoculated with a fungus called Aspergillus Oryzae, that produces a chemical that promotes B. Coccoides growth. Amazake is a rice Koji drink, whereas Shio Koji is rice Koji marinade. Creating Koji foods or drinks at home is not difficult. I would suggest avoiding soy consumption.

[A] "<>Significant changes occur in the gut microbiota during transitions between various stages of life (i.e., from childhood to adulthood to old age). A study that monitored the intestinal microbes of children from 2 weeks to 13 years of age found that B. coccoides was rarely present in the intestinal microbiota of children younger 6 months, but was more common in those older than 12 months. A similar phenomenon was also observed in commercial diet-fed pigs and rats. The researchers found that the abundance of fecal microorganisms continued to change with the age of pigs, accompanied by an

increase in the proportion of Blautia. In one study, middle-aged rats and young rats fed the same egg protein diet for 14 days showed significantly different intestinal microbiome at the end of 14 days.
<>Particularly, the middle-aged rats' relative abundance of Blautia was increased. Another study that analyzed the cecal microbiome of specific pathogen-free chicks on days 14, 28, and 42 by sequencing of the V3-V4 region of 16S rRNA gene on the Illumina MiSeq platform revealed that the abundance of Blautia increased with the age of chicks. A cross-sectional study of the stool samples of 367 healthy Japanese subjects aged 0–104 years using high-throughput sequencing of V3-V4 region of 16S rRNA gene reported that the intestinal microbiota of Japanese adults (21–69 years old) contained high abundance of Blautia and Bifidobacterium and low abundance of Bacteroides.
<>In addition, compared with the adults, the elderly showed reduced microbiome diversity and abundance of individual microbes, including a lower Blautia abundance. This phenomenon may be related to an age-related decline in immune function known as immunosenescence, accompanied by many age-related conditions that involve chronic low-level inflammation."[385.1]

[A2] "<>Background: The Japanese traditional cuisine, Washoku, considered to be responsible for increased longevity among the Japanese, comprises various foods fermented with the non-pathogenic fungus Aspergillus oryzae (koji). We have recently revealed that koji contains an abundant amount of glycosylceramide. Intestinal microbes have significant effect on health. However, the effects of koji glycosylceramide on intestinal microbes have not been studied.
<>Materials and methods: Glycosylceramide was extracted and purified from koji. C57BL/6N mice were fed a diet containing 1 % purified koji glycosylceramide for 1 week. Nutritional parameters and faecal lipid constituents were analyzed. The intestinal microbial flora of mice on this diet was investigated.
<>Results: Ingested koji glycosylceramide was neither digested by intestinal enzymes nor was it detected in the faeces, suggesting that koji glycosylceramide was digested by the intestinal microbial flora. Intestinal microbial flora that digested koji glycosylceramide had an increased ratio of Blautia coccoides. Stimulation of B. coccoides growth by pure koji glycosylceramide was confirmed in vitro.
<>Conclusions: Koji functions as a prebiotic for B. coccoides through glycosylceramide. Since there are many reports of the effects of B. coccoides on health, an increase in intestinal B. coccoides by koji glycosylceramide might be the connection between Japanese cuisine, intestinal microbial flora, and longevity."[385.2]

[B] A Blend of Bifidobacterium's reduces inflammation.

"<>Inflammatory markers such as interleukin (IL)-6 and tumour necrosis factor-alpha (TNF-α) are elevated in dialysis patients and can predict cardiovascular events and all-cause mortality. Endotoxin is an important source and also another marker of inflammation in patients with chronic kidney disease. The aim of this study was to evaluate the impact of oral probiotics on serum levels of endotoxemia and cytokines in peritoneal dialysis (PD) patients. The decline of residual renal function, peritonitis episodes, and cardiovascular events were also recorded.
<>From July 2011 to June 2012, a randomised, double-blind, placebo-controlled trial was conducted in PD patients. The intervention group received one capsule of probiotics containing 109 cfu Bifobacterium bifidum A218, 109 cfu Bifidobacterium catenulatum A302, 109 cfu Bifidobacterium longum A101, and 109 cfu Lactobacillus plantarum A87 daily for six months, while the placebo group received similar capsules containing maltodextrin for the same duration. Levels of serum TNF-α, interferon gamma, IL-5, IL-6, IL-10, IL-17, and endotoxin were measured before and six months after intervention. 39 patients completed the study (21 in the probiotics group and 18 in the placebo group).
<>In patients receiving probiotics, levels of serum TNF-α, IL-5, IL-6, and endotoxin significantly decreased after six months of treatment, while levels of serum IL-10 significantly increased. In contrast, there were no significant changes in levels of serum cytokines and endotoxin in the placebo group after six months. In addition, the residual renal function was preserved in patients receiving probiotics. In conclusion, probiotics could significantly reduce the serum levels of endotoxin, pro-inflammatory cytokines (TNF-α and IL-6), IL-5, increase the serum levels of anti-inflammatory cytokine (IL-10), and preserve residual renal function in PD patients."[386]

[B] Colonic Bacteria facilitate neuronal NMDA receptors. This means that **intelligence is precisely related to the health (microbiome) of our <u>colons</u>**, bringing new meaning to the term "Anal Retentive" originally posited by Sigmund Freud.

"<>Perturbations of the microbiota–gut–brain axis may have important consequences on the expression and activity of glutamatergic NMDA receptors and the related brain-derived neurotrophic factor (BDNF), both fundamental for neuroplasticity in brain regions, such as the hippocampus, amygdala, and cingulate cortex, all involved in stress responses. Data obtained from preclinical studies suggest that stress-related mood disorders, such as major depression and generalized anxiety, commonly diagnosed in IBD patients may be related to alterations in the saprophytic microflora homeostasis."[387]

[C] Lactobacillus Plantarum enhances myogenesis.

"<>Lactobacillus plantarum (L. plantarum) is a well-known probiotic among the ingested-microorganism probiotics (i.e., ingested microorganisms associated with beneficial effects for the host). However, few studies have examined the effects of L.

plantarum TWK10 (LP10) supplementation on exercise performance, physical fatigue, and gut microbial profile. Male Institute of Cancer Research (ICR) strain mice were divided into three groups (n = 8 per group) for oral administration of LP10 for six weeks at 0, 2.05 × 108, or 1.03 × 109 colony-forming units/kg/day, designated the vehicle, LP10-1X and LP10-5X groups, respectively.
<>LP10 significantly decreased final body weight and increased relative muscle weight (%). LP10 supplementation dose-dependently increased grip strength ($p < 0.0001$) and endurance swimming time ($p < 0.001$) and decreased levels of serum lactate ($p < 0.0001$), ammonia ($p < 0.0001$), creatine kinase ($p = 0.0118$), and glucose ($p = 0.0151$) after acute exercise challenge. The number of type I fibers (slow muscle) in gastrocnemius muscle significantly increased with LP10 treatment. In addition, serum levels of albumin, blood urea nitrogen, creatinine, and triacylglycerol significantly decreased with LP10 treatment.
<>Long-term supplementation with LP10 may increase muscle mass, enhance energy harvesting, and have health-promotion, performance-improvement, and anti-fatigue effects."[388]

[D] The Microbiome promotes exercise capacity and endurance through endocannabinoid activity & activation of TRPV1 receptors.
"<>Exercise exerts a wide range of beneficial effects for healthy physiology. However, the mechanisms regulating an individual's motivation to engage in physical activity remain incompletely understood. An important factor stimulating the engagement in both competitive and recreational exercise is the motivating pleasure derived from prolonged physical activity, which is triggered by exercise-induced neurochemical changes in the brain.
<>Here, we report on the discovery of a gut-brain connection in mice that enhances exercise performance by augmenting dopamine signalling during physical activity. We find that microbiome-dependent production of endocannabinoid metabolites in the gut stimulates the activity of TRPV1-expressing sensory neurons and thereby elevates dopamine levels in the ventral striatum during exercise. Stimulation of this pathway improves running performance, whereas microbiome depletion, peripheral endocannabinoid receptor inhibition, ablation of spinal afferent neurons or dopamine blockade abrogate exercise capacity.
<>These findings indicate that the rewarding properties of exercise are influenced by gut-derived interoceptive circuits and provide a microbiome-dependent explanation for interindividual variability in exercise performance. Our study also suggests that interoceptomimetic molecules that stimulate the transmission of gut-derived signals to the brain may enhance the motivation for exercise.[388.1]

Bacillus Subtilis (Nattō)

[A] This strange organism is inflammatory by way of the Toll-Like Receptor 4 activation.

"<>Bacillus subtilis (B. subtilis) has a variety of proposed beneficial effects for chickens, including growth promotion and disease prevention. In this study, chickens were fed a

diet containing B. subtilis for 21 days and growth performance, intestinal morphology, intestinal microbiota, immune responses, and disease resistance were investigated. After 21 days of feeding, chickens fed a diet containing B. subtilis had higher body weights. The concentrations of serum immunoglobulins IgA and IgM were significantly increased by B. subtilis in the diet. Moreover, chickens fed with B. subtilis had greater villus height (VH), shallower crypt depth (CD), and a higher VH/CD ratio in the jejunum than chickens fed a standard control diet.
<>Diet with B. subtilis can balance intestinal microbiota, facilitate an increase in beneficial bacteria, and inhibit the pathogenic bacteria after 21 days of feeding. After an Escherichia coli (E. coli) challenge, the survival rate of chickens fed with B. subtilis was 66.67%, which was significantly higher than the controls. The E. coli contents in spleens and lungs from chickens fed a diet with B. subtilis were lower than those in controls. In addition, B. subtilis can trigger the toll-like receptor 4 and cause induction of proinflammatory cytokine (Il1β, Il6, and Il8) production to develop innate immune responses in chickens. In conclusion, diets containing B. subtilis can improve growth performance, serum immunoglobulin levels, the intestinal villus-crypt system, intestinal homeostasis, immune responses, and disease resistance against E. coli in chickens."[388.2]

[B] Nattō promotes IFN-y expression.

"<>The effects of Bacillus subtilis natto on performance and immune function of dairy calves during the preweaning phase were investigated in this study. Twelve Holstein male calves 7 ± 1 d of age were randomly allotted to 2 treatments of 6 calves. The Bacillus subtilis natto was mixed with milk and fed directly to the calves. The calves were weaned when their starter intake reached 2% of their weight. Blood was collected and IgA, IgE, IgG, IgM, and cytokine levels in the serum of all the calves were determined. The results showed that Bacillus subtilis natto increased general performance by improving the average daily gain and feed efficiency and advanced the weaning age of the calves. No difference was observed in serum IgE, IgA, and IgM, whereas serum IgG was higher in the Bacillus subtilis natto-supplemented calves than in the control calves. <>Furthermore, calves fed with Bacillus subtilis natto were found to secrete more IFN-γ, but tended to produce less IL-4 than did the control calves, although serum IL-6 and IL-10 were not affected. This study demonstrated that Bacillus subtilis natto did not stimulate IgE-mediated allergic reactions, but increased serum IgG and IFN-γ levels in the probiotic-fed calves. We propose that the viable probiotic characteristics of Bacillus subtilis natto benefit calf immune function."[388.2.1]

2'-Fucosyllactose

This beneficial oligosaccharide in human breast milk appears to be an excellent antioxidant and neurotrophic chemical. It is now being synthesized by laboratory.

[A] 2-FL enhances bDNF expression.

“<>2'-Fucosyllactose (2'-FL) is a major oligosaccharide in human milk and is present at trace levels in cow milk. 2'-FL reduces inflammation in the gastrointestinal tract. Its action in the central nervous system has not been well characterized. The purpose of this study is to determine 2'-FL-mediated neural protection and repair in culture and stroke brain. In rat primary cortical neuronal cultures, 2'-FL significantly antagonized N-methyl-D-aspartate (NMDA) or glutamate-mediated changes in ATP production, MAP2 immunoreactivity, and TUNEL. The influx of Ca++ (Ca++i) was examined in primary cortical neurons expressing GCaMP5, an endogenous calcium probe. NMDA increased Ca++i; 2'-FL significantly attenuated this reaction.
<>In a rat middle cerebral artery occlusion model of stroke, we found that intracerebroventricular pretreatment or oral posttreatment with 2'-FL significantly reduced brain infarction, mitigated microglial activation, improved locomotor activity, and upregulated brain-derived neurotrophic factor (BDNF) expression. Post-stroke delivery of 2'-FL increased bromodeoxyuridine (BrdU) labeling in the perilesioned area. These BrdU cells co-expressed NeuN, or nestin, or GFAP. Using subventricular Matrigel cultures, we demonstrated that 2'-FL increased cell migration from subventricular zone explant. This response was reduced by anti-BDNF blocking antibody. In conclusion, our data suggest that 2'-FL has neuroprotective action through inhibition of Ca++i, inflammation, and apoptosis. Posttreatment with 2'-FL facilitates neural repair in stroke brain.”[388.3]

[B] 2-FL, like Lactobacillus Rhamnosus, activates the Vagus Nerve to exert neuromodulatory effects.

“<>2′-fucosyllactose (2′-FL) is an abundant human milk oligosaccharide (HMO) in human milk with diverse biological effects. We recently reported ingested 2′-FL stimulates central nervous system (CNS) function, such as hippocampal long term potentiation (LTP) and learning and memory in rats. Conceivably the effect of 2′-FL on CNS function may be via the gut-brain axis (GBA), specifically the vagus nerve, and L-fucose (Fuc) may play a role.
<>This study had two aims: (1) determine if the effect of ingested 2′-FL on the modulation of CNS function is dependent on the integrity of the molecule; and (2) confirm if oral 2′-FL modified hippocampal LTP and associative learning related skills in rats submitted to bilateral subdiaphragmatic vagotomy.
<>Results showed that 2′-FL but not Fuc enhanced LTP, and vagotomy inhibited the effects of oral 2′-FL on LTP and associative learning related paradigms. Taken together, the data show that dietary 2′-FL but not its Fuc moiety affects cognitive domains and improves learning and memory in rats. This effect is dependent on vagus nerve integrity, suggesting GBA plays a role in 2′-FL-mediated cognitive benefits.”[388.3.1]

Kefir

Kefir promotes muscle performance, and glycogen content, at the cost of increased Bacteroidetes growth. This may hint to the positive performance enhancing effects of Bacteroidetes growth.

"<>The present study evaluated the potential beneficial effect of kefir (KF) against fatigue. Furthermore, the composition of the gut microbiota is related to health benefits in the host; therefore, the study also investigated the effect of KF on the gut microbiota composition. Male ICR mice from four groups (n = 8 per group) were orally administered KF once daily for four weeks at 0, 2.15, 4.31, and 10.76 g/kg/day and were designated as the vehicle, KF-1X, KF-2X, and KF-5X groups, respectively. The gut microbiota was analyzed using 16S rRNA gene sequencing.
<>The results showed a significant clustering of cecum after treatment in the vehicle, KF-1X, KF-2X, and KF-5X groups. The KF-2X and KF-5X groups showed a decreased Firmicutes/Bacteroidetes ratio compared with the vehicle group. In addition, anti-fatigue activity and exercise performance were evaluated on the basis of exhaustive swimming time, forelimb grip strength, and levels of serum lactate, ammonia, glucose, blood urea nitrogen (BUN), and creatine kinase (CK) after a swimming exercise. The exhaustive swimming time for the KF-1X, KF-2X, and KF-5X groups was significantly longer than that for the vehicle group, and the forelimb grip strength of the KF-1X, KF-2X, and KF-5X groups was also significantly higher than that of the vehicle group. KF supplementation also decreased serum lactate, ammonia, BUN, and CK levels after the swimming test.
<>However, tissue glycogen content, an important energy source for exercise, increased significantly with KF supplementation. Thus, KF supplementation can alter the gut microbiota composition, improve performance, and combat physical fatigue."[388.4]

Kimchi

Kimchi reduces muscle atrophy factors MuRF-1 / Atrogin-1.

"<>Cancer cachexia is a syndrome accompanying weight loss, skeletal muscle atrophy, and loss of adipose tissue in patients with advanced cancer. Since interleukin-6 (IL-6) is one of core mediators causing cancer cachexia and kimchi can modulate IL-6 response, we hypothesized dietary intake of kimchi can ameliorate cancer cachexia. In this study, we studied preemptive administration of kimchi can ameliorate mouse colon carcinoma cells colon (C26) adenocarcinoma-induced cancer cachexia and explored anti-cachexic mechanisms of kimchi focused on the changes of muscle atrophy, cachexic inflammation, and catabolic catastrophe.
<>As results, dietary intake of kimchi significantly attenuated the development of cancer cachexia, presented with lesser weight loss, higher muscle preservation as well as higher survival from cancer cachexia in mice. Starting from significant inhibition of IL-6 and its signaling, kimchi afforded significant inhibition of muscle specific ubiquitin-proteasome system including inhibition of atrogin-1 and muscle ring finger protein-1 (MuRF-1) with other muscle related genes including mitofusin-2 (Mfn-2) and PGC-1α. Significant

inhibition of lipolysis gene such as adipose triglyceride lipase (ATGL) and hormone-sensitive ligase (HSL) accompanied with significant induction of fatty acid synthase (FAS) and sterol response element binding protein 1 (SREBP1) was achieved with kimchi.
<>As gene regulation, IL-6 and their receptor as well as Janus kinase 2 (JAK2) and signal transducer and activator of transcription 3 (STAT3) were significantly attenuated with kimchi. In conclusion, dietary intake of cancer preventive kimchi can be an anticipating option to ameliorate cancer cachexia via suppressive action of IL-6 accompanied with decreased muscle atrophy and lipolysis."[388.5]

[See: Anti-Cycle Supplementation: Kombucha]

[See: Pro-Cycle Supplementation Bacillus Coagulans]

Microorganism Intelligence

Quorum Sensing

Quite impressively, as explained by Stephan Schauder and Bonnie L. Bassler, microorganisms are capable of communicating with each other by using chemical excretions as words, and many bacteria are capable of multilingual chemical-language.

"<>Bacteria communicate with one another using chemical signaling molecules as words. Specifically, they release, detect, and respond to the accumulation of these molecules, which are called autoinducers. Detection of autoinducers allows bacteria to distinguish between low and high cell population density, and to control gene expression in response to changes in cell number. This process, termed quorum sensing, allows a population of bacteria to coordinately control the gene expression of the entire community.
<>Quorum sensing confuses the distinction between prokaryotes and eukaryotes because it allows bacteria to behave as multicellular organisms, and to reap benefits that would be unattainable to them as individuals. Many bacterial behaviors are regulated by quorum sensing, including symbiosis, virulence, antibiotic production, and biofilm formation. Recent studies show that highly specific as well as universal quorum sensing languages exist which enable bacteria to communicate within and between species.
<>Finally, both prokaryotic and eukaryotic mechanisms that interfere with bacterial quorum sensing have evolved. Specifically, the secretion of enzymes that destroy the autoinducers, and the production of autoinducer antagonists, are used by competitor bacteria and susceptible eukaryotic hosts to render quorum sensing bacteria mute and deaf, respectively. Analogous synthetic strategies are now being explored for the development of novel antimicrobial therapies."
<>Bacteria in communities convey their presence to one another by releasing and responding to the accumulation of chemical signaling molecules called autoinducers.

This process of intercellular communication, called quorum sensing, was first described in the bioluminescent marine bacterium Vibrio fischeri. V. fischerilives in symbiotic associations with a number of marine animal hosts. In these partnerships, the host uses the light produced by V. fischeri for specific purposes such as attracting prey, avoiding predators, or finding a mate.
<>In exchange for the light it provides,V. fischeri obtains a nutrient-rich environment in which to reside. A luciferase enzyme complex is responsible for light production in V. fischeri. Bioluminescence only occurs when V. fischeri is at high cell number, and this process is controlled by quorum sensing. Specifically, the production and accumulation of, and the response to, a minimum threshold concentration of an acylated homoserine lactone (HSL) autoinducer regulates density-dependent light production in V. fischeri, and enables V. fischeri to emit light only inside the specialized light organ of the host but not when free-living in the ocean.
<>The reason for this is twofold. First, only under the nutrient-rich conditions of the light organ can V. fischerigrow to high population densities, and second, trapping of the diffusible autoinducer molecule in the light organ with the bacterial cells allows it to accumulate to a sufficient concentration thatV. fischeri can detect it."
↓ continued
"<>All of the quorum sensing systems we have described so far rely on the precise recognition of an autoinducer by its cognate detector. The tight specificity inherent in these communication systems is presumably required to prevent the bacteria from being confused by noise. Further, it allows them to keep their conversations private, i.e., within their own species. However, recent studies suggest that bacteria may have evolved multiple languages that serve different purposes. It appears that many bacteria possess a species-specific language as well as a species-nonspecific language. These findings imply that bacteria can assess their own population numbers and also the population density of other species of bacteria in the vicinity. Furthermore, distinct responses to the intraspecies and interspecies signals allow a particular species of bacteria to properly modulate its behavior depending on whether it makes up a majority or a minority of any given consortium."[388.5.1]

Extracellular vesicles

Extracellular vesicles (EVs) are nano sized particles (cargo) that include fatty acids, neurotransmitters, proteins, microRNA's, and many other materials, secreted from cells such as neurons, and more impressively, beneficial bacteria in our intestinal microbiome[1]. EVs secreted by intestinal bacteria are absorbed through *endocytosis* in our intestines[2], which is a process where small intestine epithelial cells "engulf" and absorb molecules, some of which interact with immune cells to exert a systemic immunological response, and some of which likely reach the brain through *transcytosis*[3], a process in which these molecules traverse through the cell thereby passing into circulation.

Quite interestingly, the EVs probiotics secrete, specifically Lactobacillus strains, directly affect the brain and protect it from degeneration by enhancing SIRT1 and bDNF

activity[4]-[5], proving that this genus of bacteria is one of the greatest protectors of human cellular health against illness and aging. We should therefore be hesitant to eat anything we see, or crave, considering it could harm our dear microscopic family, and shorten our lifespan.

[1] "<>Although probiotics are currently in the center of interest of pharmaceutical concerns, more and more research focuses on searching for alternatives to these classically used products. Difficulties in maintaining the viability of probiotics in commercial products and the fact that the viability of these microorganisms is not always necessary to obtain therapeutic effects have led to the concept of postbiotics.
<>Postbiotics are a mixture of metabolic products or non-viable fragments of probiotics that have a beneficial effect on the functioning of the human body. Despite the fact that research on postbiotics is still in its infancy, a number of health-promoting properties of these new products have already been demonstrated (maintenance of the proper structure of the resident microbiota, strengthening the host epithelial barrier, modulation of the local and systemic immune response, or increase of the host metabolic activity). As non-viable elements of probiotics, postbiotics present their strictly defined technological properties and thus represent a promising tool for obtaining therapeutic effects. These parameters include a favorable level of absorption and distribution of postbiotics and the lack of risk to spread resistance mechanisms, as documented between probiotics and microbiota or pathogens.
<>In 2021, the International Scientific Association of Probiotics and Prebiotics established a new definition of postbiotic as a "preparation of inanimate microorganisms and/or their components that confers a health benefit on the host". The use of the word 'components' was made because the whole microbial cells are not always required to present health-promoting activity and such an impact may be related to the presence of cellular structures produced by probiotics. The above modification of the meaning of the term 'postbiotic' has opened a new avenue for many new categories of these preparations, including probiotic extracellular vesicles.
<>Extracellular vesicles (EVs) are nanoscale lipid particles secreted by virtually every type of living cell. For this reason, the use of various nomenclature in the description of these structures is frequent. This richness in the nomenclature of the vesicles is related to their physical properties (mostly size), the way they are formed, or the cells that secrete them.
<>In order to standardize the nomenclature as much as possible, in accordance with the recommendations of the International Society for Extracellular Vesicles, in this review, we will use the term "extracellular vesicles". This is a collective term classically referring to various types of small compartments released from cells, which are surrounded by a lipid bilayer and incapable of spontaneous replication. The main function of EVs is the transport of various classes of macromolecules, including lipids, polysaccharides, proteins, and nucleic acids.
<>Through this cargo, these structures perform a number of key functions in microorganisms, including long-distance transport of nutrients, protection against environmental stressors, or communication during microorganism–microorganism or

microorganism–host interactions. The importance of EVs in the virulence of many life-threatening pathogens is well known and widely described in the literature. Much less is reported with respect to the health-promoting effect of EVs secreted by non-pathogenic microorganisms, including probiotics. For the last few years, however, awareness on probiotic EVs as a very promising therapeutic platform is growing rapidly. This seems to be strictly related with both the ability of EVs to carry many different bioactive macromolecules and with nanometric dimensions of these structures."[388.6]

[2] "<>Extracellular vesicles (EVs) secreted from probiotics, defined as live microorganisms with beneficial effects on the host, are expected to be new nanomaterials for EV-based therapy. To clarify the usability of probiotic-derived EVs in terms of EV-based therapy, we systematically evaluated their characteristics, including the yield, physicochemical properties, the cellular uptake mechanism, and biological functions, using three different types of probiotics: Bifidobacterium longum, Clostridium butyricum, and Lactobacillus plantarum WCFS1. C. butyricum secreted the largest amounts of EVs, whereas all the EVs showed comparable particle sizes and zeta potentials, ranging from 100 to 150 nm and −8 to −10 mV, respectively.
<>The silkworm larvae plasma assay indicated that these EVs contain peptidoglycan that activates the host's immune response. Moreover, a cellular uptake study of probiotic-derived EVs in RAW264.7 cells (mouse macrophage-like cells) and DC2.4 cells (mouse dendritic cells) in the presence of inhibitors (cytochalasin B, chlorpromazine, and methyl-β-cyclodextrin) revealed that probiotic-derived EVs were mainly taken up by these immune cells via clathrin-mediated endocytosis and macropinocytosis.
<>Furthermore, all the probiotic-derived EVs stimulated the innate immune system through the production of inflammatory cytokines (TNF-α and IL-6) from these immune cells, clarifying their utility as a novel adjuvant formulation. These findings on probiotic-derived EVs are valuable for understanding the biological significance of probiotic-derived EVs and the development of EV-based immunotherapy."[388.7]

[3] "<>In general, bacterial EVs can harbor a variety of neurotransmitters as their cargo, including dopamine, serotonin, noradrenaline and enzymes contributing to synthesis of these molecules. Bacterial EVs can also harbor short chain fatty acids that are able to influence the function of neurons and microglia. *Bacteroidetes*, one of the major bacterial phyla constituting the human gut microbiota, are known to produce enzymes aiding the digestion of nutrients and send them to the gut lumen *via* EV secretion. These enzymes include hydrolases that degrade complex carbohydrates, inositol polyphosphatases that break down dietary phytate to phosphates, inositol phosphates and inositol.
<>The commensal *Bacteroides fragilis* has been reported to secrete EVs containing neurotransmitter gamma-aminobutyric acid (GABA) and its precursors glutamate and α-ketoglutarate, while pathogenic *Bacteroides fragilis* has been reported to secrete EVs embedded with histidine decarboxylase, an enzyme catalyzing histamine synthesis"
"<>While bacterial EV cargo can reach the cells of biological barriers through different methods of endocytosis, intact bacterial EVs have been suggested to cross epithelial and endothelial layers using paracellular and transcellular routes. Bacterial EVs passing

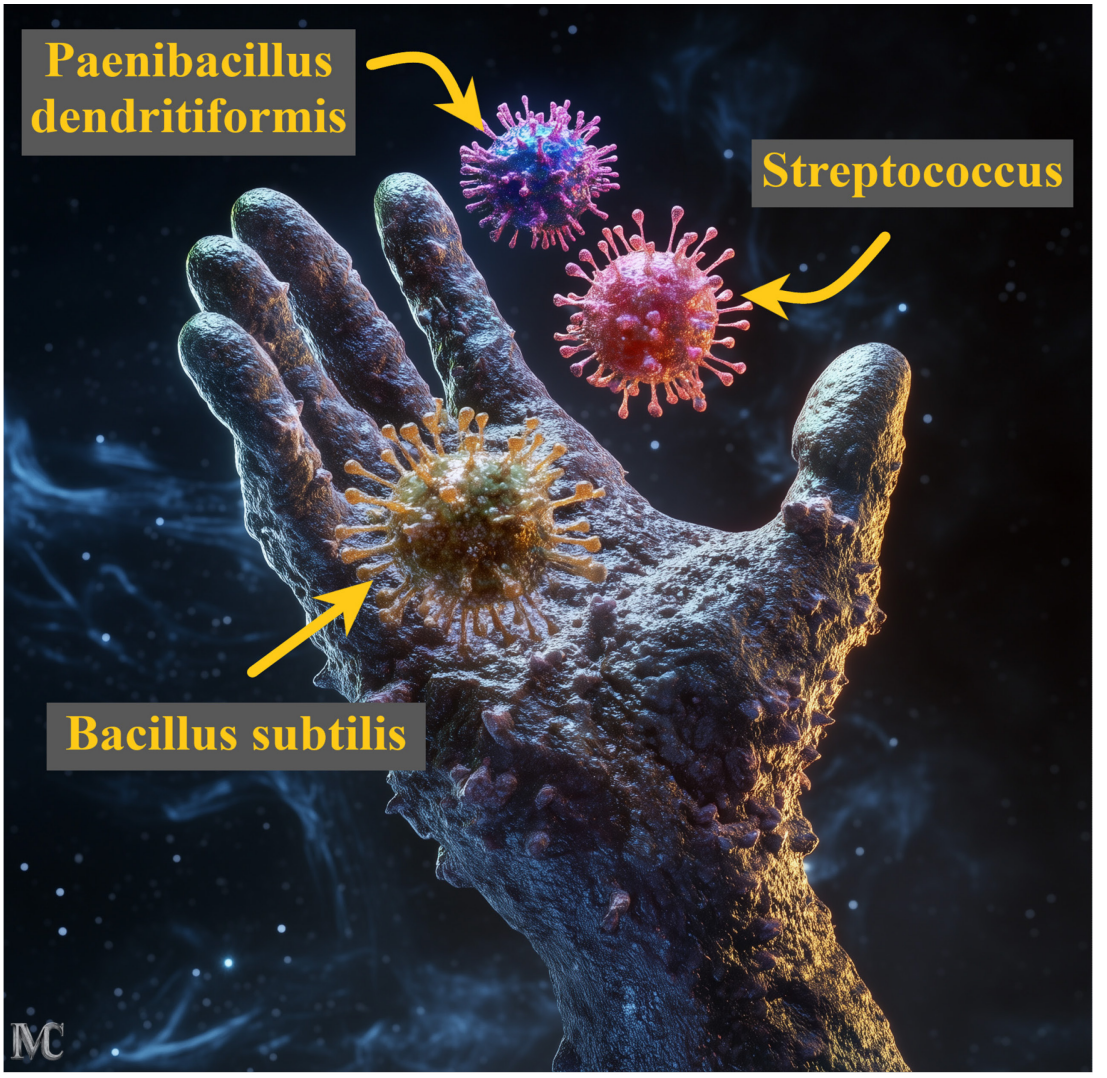
through the intestinal barrier and entering circulation is supported by findings of gut microbiota-associated EVs in dendritic cells of lamina propria, urine, and blood.
<>Moreover, it has been reported that in mice, bacterial EVs in blood represent the gut microbiome composition of the host. To pass through the gut epithelial layer, EVs can plausibly use transcellular transmigration through caveolae-mediated endocytosis or paracellular transmigration, where EVs pass through the intestinal barrier between the epithelial cells. However, the routes human gut microbiota EVs take to pass the gut epithelia likely differ between different species and utilize both transcellular and paracellular routes."[388.8]

[4] "<>Mounting evidence suggests that probiotics are beneficial for treating Alzheimer's disease (AD). However, the mechanisms by which specific probiotics modify AD pathophysiology are not clearly understood. In this study, we investigated whether Lactobacillus paracasei-derived extracellular vesicles (Lpc-EV) can directly act on neuronal cells to modify amyloid-beta (Aβ)-induced transcriptional changes and Aβ pathology in the brains of Tg-APP/PS1 mice.
<>Lpc-EV treatment in HT22 neuronal cells counteracts Aβ-induced downregulation of Brain-derived neurotrophic factor (Bdnf), Neurotrophin 3 (Nt3), Nt4/5, and TrkB receptor, and reverses Aβ-induced altered expression of diverse nuclear factors, including the downregulation of Methyl-CpG binding protein 2 (Mecp2) and Sirtuin 1 (Sirt1). Systematic siRNA-mediated knockdown experiments indicate that the upregulation of Bdnf, Nt3, Nt4/5, and TrkB by Lpc-EV is mediated via multiple epigenetic factors whose activation converges on Mecp2 and Sirt1.
<>In addition, Lpc-EV reverses Aβ-induced downregulation of the Aβ-degrading proteases Matrix metalloproteinase 2 (Mmp-2), Mmp-9, and Neprilysin (Nep), whose upregulation is also controlled by MeCP2 and Sirt1. Lpc-EV treatment restores the downregulated expression of Bdnf, Nt4/5, TrkB, Mmp-2, Mmp-9, and Nep; induces the upregulation of MeCP2 and Sirt1 in the hippocampus; alleviates Aβ accumulation and neuroinflammatory responses in the brain; and mitigates cognitive decline in Tg-APP/PS1 mice.
<>These results suggest that Lpc-EV cargo contains a neuroactive component that upregulates the expression of neurotrophic factors and Aβ-degrading proteases (Mmp-2, Mmp-9, and Nep) through the upregulation of MeCP2 and Sirt1, and ameliorates Aβ pathology and cognitive deficits in Tg-APP/PS1 mice."[388.9]

[5] "<>Gut microbiota play a role in regulating mental disorders, but the mechanism by which gut microbiota regulate brain function remains unclear. Gram negative and positive gut bacteria release membrane-derived extracellular vesicles (EVs), which function in microbiota-host intercellular communication.
<>In the present study, we investigated whether Lactobacillus plantarum derived EVs (L-EVs) could have a role in regulating neuronal function and stress-induced depressive-like behaviors. HT22 cells treated with the stress hormone glucocorticoid (GC; corticosterone) had reduced expression of Bdnf and Sirt1, whereas L-EV treatment reversed GC-induced decreased expression of Bdnf and Sirt1. The siRNA-mediated

knockdown of Sirt1 in HT22 cells decreased Bdnf4, a splicing variant of Bdnf, and Creb expression, suggesting that Sirt1 plays a role in L-EV-induced increase of BDNF and CREB expression. Mice exposed to restraint for 2-h daily for 14 days (CRST) exhibited depressive-like behaviors, and these CRST-treated mice had reduced expression of Bdnf and Nt4/5 in the hippocampus.
<>In contrast, L-EV injection prior to each restraint treatment blocked the reduced expression of Bdnf and Nt4/5, and stress-induced depressive-like behaviors.
<>Furthermore, L-EV treatment in CRST-treated mice also rescued the reduced expression of Bdnf, and blocked stress-induced depressive-like behaviors. These results suggest that Lactobacillus derived EVs can change the expression of neurotropic factors in the hippocampus and afford antidepressant-like effects in mice with stress-induced depression."[388.10]

The Good, the Bad, and the Ugly (Bacteria)



In the superb research paper formulated by Larisa N. Ikryannikova, Leonid K. Kurbatov, Surinder M. Soond,1 and Andrey A. Zamyatnin, Jr. below, we learn that bacteria are capable of displaying a form of "aggression" or "hostility" called Allolysis, where they break down or *lyse* the cell walls of other microorganisms, thereby killing them, resulting in reduced competitiveness in the environment i.e. greater resources and space.

Certain bacteria are capable of secreting "allolysis toxins" that are specifically designed to harm their neighboring sibling cells, or their own cells (altruism), and some bacteria are capable of cannibalizing their own cells such as Bacillus Subtilis. Although certain types of bacterial Allolysis may contribute to biofilm integrity, it is clear that the general purpose of the phenomenon is to enhance the cellular fitness or competitive advantage of a particular microorganism, at the cost of another. Is this not a potential proof that selfishness, and selflessness originated from the earliest and most simplistic lifeforms on Earth? And if that is the case, then what does it mean for microorganism diversity in a human microbiome? Is it possible that they influence our behavior through mechanisms beyond Extracellular Vesicles? Could it be possible that there are noticeable microbiome differences between a human killer and a human altruist, or is that a question too strange to ask? Only time and research will be able to decipher the true influence of our intestinal florae, that of which is a community of life within life.

[Note: I have added the words "Good", "Bad", & "Ugly" to this research article as I find them be apropos descriptors]

Introduction

"<>Bacterial allolysis is an interesting phenomenon which has been under discussion for the last 15 years. It was first defined by Guiral et al. to describe the phenomenon of cell demise in a subset of a bacterial population induced by other cells of the same species. The introduction of this special term was prompted by a necessity to differentiate this phenomenon from other types of cell lysis, such as heterolysis (or predation), which is directed against other unrelated species, or autolysis (which describes the self-destruction of cells). In the case of bacteria, the terms "fratricide" and "cannibalism" are often respectively associated with Streptococcus pneumoniae and other members of the Streptococcus genus and when speaking of "kin killing" in Bacillus subtilis populations. The term "siblicide" is also used occasionally, as well as "sobrinicide", to specify the type of killing observed between closely related species from the same phylotype. <>Allolysis has been observed for a few species only (as mentioned above) and it has been suspected to occur in a case of some other respective genera and species like enterococci or Paenibacillus dendritiformis. It could be assumed that this phenomenon could arise and be related to the fundamental evolutionary processes inherent to all or at least most microorganisms. However, it is quite surprising that over the past two decades since the first mention of the kin killing phenomena that our knowledge still remains limited and within the paradigms presented by a few well-studied species. As was noted by Popp and Mascher in their very recent review, a fundamental shift and breakthrough in this area will probably require a change in the perception of microorganisms from

single, planktonic cells to the conception of bacterial communities consisting of different sub-populations with distinct functions.

<>The biological role of allolysis is not yet completely understood and has raised a number of interesting questions for researchers. Certainly, the first question of interest is related to the purpose of this phenomenon—Why do cells kill their own siblings? The next question revolves around the mechanistic regulation of this process—How do "predator" cells that are successful in killing their isogenic neighbors confer resistance to this type of death, and what are the protective barriers? What is the basis by which the toxins are made by the "predators"? Are these toxins routinely used in normal processes within the cell or are they more specialized in their design, role, and specificity for killing siblings?"

↓ continued

"<>Bacterial allolysis belongs to a class of programmed cell death (PCD) phenomena in prokaryotes. PCD is defined as an active, precisely regulated process for any form of cell death mediated by intracellular genetic programs. Towards the end of the 20th century, it was discovered that some forms of PCD (including apoptosis) exists not only in multicellular animals, but also in plants, lower eukaryotes, and yeast cells. PCD in prokaryotes remained questionable for a long time; however, the facts supporting this have been accumulating over time and which demonstrate that microorganisms often behave as members of a multicellular community, adding support to the idea that the analogues of PCD exist in bacteria.

<>Indeed, the ideas of altruistic self-killing or fratricide seem meaningless when applied to a single cell, as one cell cannot benefit from its own death. However, in their natural habitat, microorganisms do not usually exist as planktonic cells, they are social organisms and many of them can switch from unicellular to multicellular organization such as microbial colonies, biofilms and aggregates. "Multicellular" life styles can offer many advantages, such as increased protection against hostile environments, increased genetic diversity and improved food availability and is characterized by clear lines of communication between the members (e.g., quorum sensing) and differentiation into the specialized subpopulations ("the division of labor") as well as complex patterns of collective behavior (shared hunting, collective resistance to antibiotics, etc.). In the "multicellular" bacterial community, sacrificing part of the population can be a way to sustain the survival of the remaining cells."

The Good: "Forced Suicide" in Paenibacillus dendritiformis

"<>Paenibacillus dendritiformis is an interesting bacterial species marked by the complex spatial organization of its colony, which can form different patterns of growth on semi-solid agar such as chiral branches, swirls, and vortices. It was observed that the sibling P. dendritiformis bacterial colonies grown on low-nutrient agar medium mutually inhibited the growth of each other. The factor responsible for the killing activity was purified from agar between growing competing colonies and named the "sibling-lethal factor" (Slf). Slf, a 12-kDa polypeptide, was shown to be derived from a precursor protein termed DfsB (dendritiformis sibling bacteriocin) which was cleaved by the serine protease

subtilisin giving rise to its active form. <>Subtilisin is another important factor unveiled to seemingly trigger the threshold response. It is secreted by P. dendritiformis into the environment and can be detected around the growing colonies, where its proteolytic activity may likely break down proteins to provide more accessible nutrient sources to the bacteria. As the concentration of subtilisin was proportional to the cell density it may therefore serve as a quorum sensor to control the growth of cells. When grown on low-nutrient agar medium (below a threshold concentration), subtilisin promoted colony growth and expansion. However, at the interface between competing colonies, the local concentration of subtilisin increased sharply, resulting in the secretion of an active form of Slf which lyses cells within the zone between the two colonies.
<>It was found that Slf was lethal to P. dendritiformis but not to other bacteria, even closely related ones, suggestive of the strict and narrow specificity of this toxin towards its own species. It is also worth noting that while the production of Slf is induced by a sibling colony (via secreted subtilisin), the protein factor itself can be derived from the host, suggesting that this can be considered closer to induced suicide rather than direct fratricide.
<>Clearly, there is a need for further studies concerning this interesting bacterium, as it remains unclear what other growth conditions (besides starvation) cause the competitive capacity of single colonies to be manifested, or a detailed mechanism through which sensitive cells undergo cell death. Moreover, the most interesting question of how the bacterial cell protects itself from the death-inducing activity of its own toxin is also eagerly awaited."

The Bad: Fratricide in Streptococcus & "Siblicide" in Enterococcal

"<>In bacterial allolysis, the most characterized and studied model of cell death is the streptococcal fratricide phenomenon. As there are earlier excellent reviews on this topic which provide the basic principles of fratricide, we will try to bring into focus new findings obtained in recent years and extend the context of such findings. Generally, fratricide in S. pneumoniae is associated with a cascade of events linked to entering a state of competence closely linked to the genetic transformation process. Competence in S. pneumoniae can be triggered by some environmental and physiological signals, such as cell density, changes in pH, or the presence of antibiotics during exponential growth, in a process that is governed by quorum sensing (QS).
<>Changes in such conditions lead to an extracellular accumulation of the QS signal - the competence-stimulating peptide (CSP) or a pheromone, ComC. ComC is secreted from the cytoplasm by the ComAB transport system. Upon reaching an extracellular threshold concentration, it can interact with its cognate receptor at the cell surface, the transmembrane domain of ComD histidine kinase, leading to its activation. Consequently, activated ComD phosphorylates the cytoplasmic response regulator ComE, which in turn upregulates the expression of the 20 or so "early" competence (com) genes. One of these early com genes encodes the alternative sigma factor X (ComX) that activates the transcription of the "late" com genes, including the genes necessary for DNA binding, uptake, processing, and integration. It was noted that the

number of CSP-responsive genes in S. pneumoniae (over 100) are essentially excessive in the numbers required to permit the process of DNA transformation, suggestive of some being involved in other cellular processes beyond the molecular machinery required for DNA uptake and recombination.

<>Of relevance is one processes triggered by the induction of the competent state, which includes the expression of protein toxins (allolysis toxins or fratricines) that are deadly to neighboring sibling cells. To avoid the total death of the whole population, the protein that confers resistance (ComM) and provides protection against self-killing is also stimulated during the early stage of competence. Only the cells failing to become competent and therefore not protected by ComM undergo lysis by fratricide toxins. The mechanistic reasons for why some of the cells do not respond to CSP signals, while the rest of the population develops the competent state, are not exactly known and form the basis of on-going research. However, it is well known that isogenic bacteria growing under identical conditions do not necessarily display the same pattern of gene expression during competence. This phenomenon is termed "bistability", and is not associated with genome rearrangements or mutations, but alternatively involves reversible switching between varying states of competency in the absence of any genetic modification.

<>Consequently, it is possible that bistability gives rise to a mixed population of competent "predators" and non-competent target cells. Another potential source of heterogeneity is due to different streptococci cells producing different pheromones. Strains producing the same pheromones constitute the pherotype group. Pheromones can effectively induce a state of competence only within their pherotypes, so that within a mixed natural population of cells the members of one pherotype developing the state of competence the quickest can have a survival advantage over streptococci originating from other pherogroups, who are unable to accept CSP signals and thus remain non-competent. In addition to bistability and pherotype diversity, the heterogeneous physico-chemical conditions existing inside pneumococcal colonies or within biofilms are believed to be important."

↓ continued

"<>A mechanism similar to streptococcal fratricide was also suggested for the phylogenetic neighbors of streptococci, namely enterococci. It is worth noting that in contrast to streptococcal fratricide, which has been extensively studied and characterized, the existence of such a phenomenon in the instance of enterococci is less clear and is rather a hypothesis deduced from a number of indirect observations. Here, an alternate hypothesis of altruistic suicide or any other form of programmed cell death may remain a possibility.

<>The phenomenon of "siblicide" was observed in some clinical isolates of enterococci (*Enterococcus faecalis* and *Enterococcus faecium*), that, while growing as a colony ("stabs" into agar) on solid media, exhibited a growth-inhibitory effect on a lawn composed of the same strain. This effect was attributed to the production of a class IIa bacteriocin (enterocin) (MC4-1) encoded on a conjugative, highly transferable, pheromone-responding, multiple antibiotic-resistance plasmid pAMS1. The lack of immunity against its own bacteriocin was explained by a difference in the expression levels of both the bacteriocin MC4-1 and corresponding immunity genes in the producer

cells (a stabbed colony in early stationary phase growing under limited conditions) and target cells (a lawn in early exponential stage of growth)."

The Ugly: Cannibalism in Bacillus subtilis

"<>The allolysis-like phenomena in B. subtilis is associated with the sporulation process. When exposed to environmentally stressful conditions, for example starvation, this microorganism initiates a complex survival strategy which is called sporulation leading to the formation of endospores that are very resistant to adverse environmental conditions. It allows B. subtilis to survive and wait for favorable conditions for growth. The entrance into the sporulation pathway is a multistep process associated with a diversification into distinct sub-populations of specialized cell types that try to extract different types of nutrients from the environment.

<>The sporulation process starts with the activation of the DNA-binding protein Spo0A, which is considered a key regulator of sporulation, and also biofilm formation and cannibalism. This protein is activated by phosphorylation and controls the transcription of around 120 genes. A portion of these genes involved in biofilm formation and production of cannibalism toxins (see below) have high-affinity Spo0A binding sites and require only low levels of phosphorylated Spo0A (Spo0A-P), while other genes involved in the process of spore formation depend on higher Spo0A-P levels.
<>Sporulation is a very time and energy consuming process that becomes irreversible during certain stages of growth. In order to avoid this unprofitable burden, B. subtilis tries to delay sporulation as long as possible and employs different strategies to achieve this. One such "last delay" strategy (called cannibalism) involves the production and secretion of peptide toxins which are able to lyse sensitive siblings. Cannibalism toxins, as well as the immunity factors protecting the "cell-cannibals", are probably produced by the sub-population of cells which have entered the sporulation pathway but have not yet completed it. The lysed cells are thought to provide nutrients for the cannibals to continue vegetative growth."[388.11]

Panspermia & Viruses

We evolved from unicellular microorganisms, who developed mitochondria from the cellular enslavement of aerobic bacteria, and this evolutionary mutation was only made possible through innumerable genetic mutations caused by viral infections over billions of years. Unfortunately, the modern science taught in schools and colleges often conflate the process of Natural selection with true evolutionary sciences i.e. the true cause of genetic mutations. Natural selection is not capable of explaining the steady evolution of multicellular organisms into complex forms of life such as humans and plants, even given a massive amount of time, and random probability, yet it is most often used as a tool to attack theistic thought, to prove that *heritable traits increase or decrease survivability* and that *heritable traits result in complexity of life*, but it cannot explain the origins of

life, nor can it explain the initiation of massive mutations required in the evolution of complex lifeforms. Life requires adaptation, but we have not reached our natural (flesh-based) evolutionary point through randomness, it is instead viruses that have shaped us into what we have become, the infective programs that have given our ancestors, from the earliest cells, to the earliest mammals, the novel or altered genetic information to change, to adapt—to mutate.

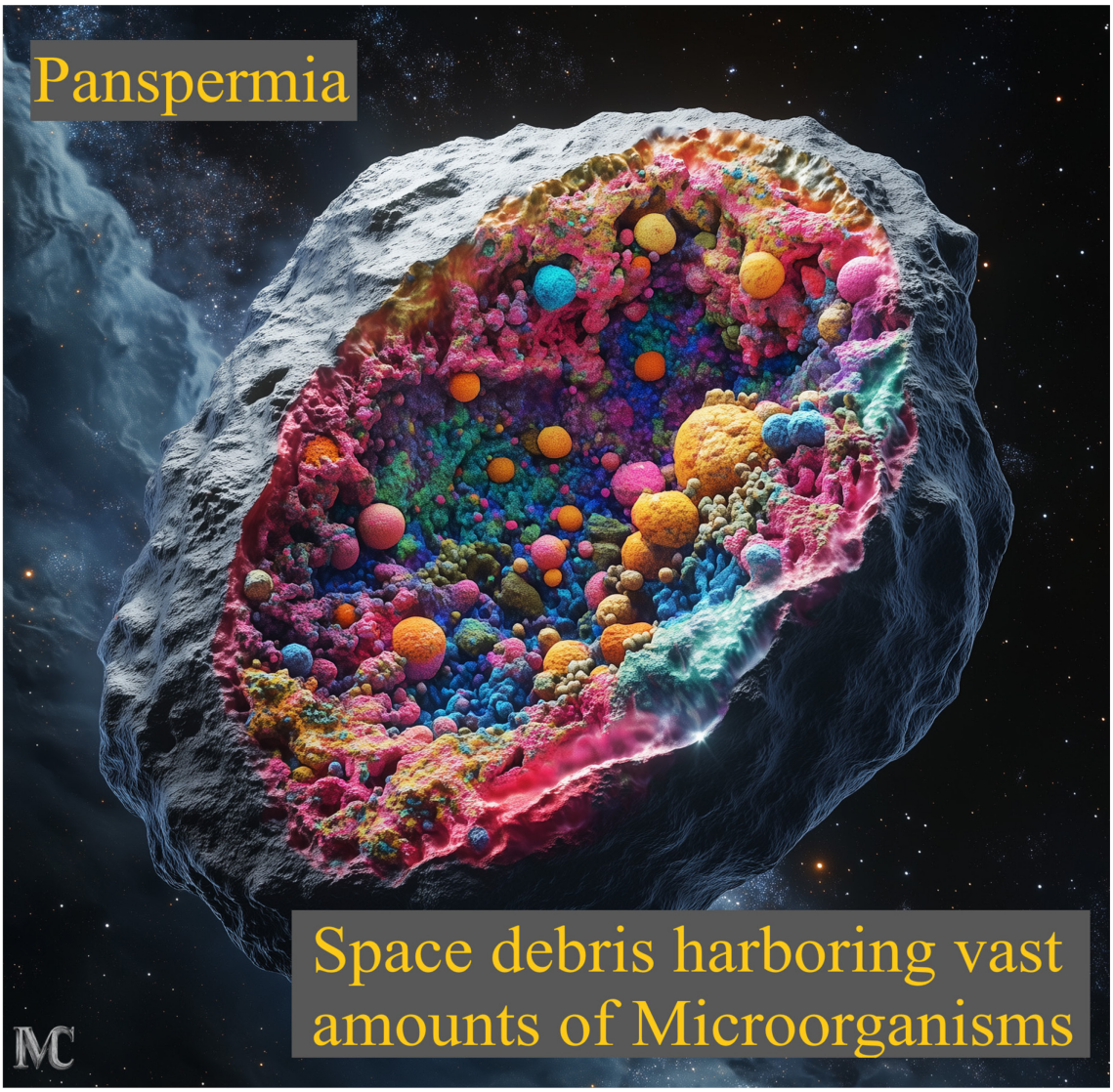
It is strange that many viruses in existence today cause harm to us, rather than causing beneficial adaptation, but this may be due to the precise *spread* of specific viruses, rather than *origin*, for example it has been said that the Marburg virus, which is from the same family as the Ebola virus, was originally considered for use as a bioweapon by the Soviet Republic. Regardless, it is logical to suggest without indirect speculation that the viruses we will encounter tomorrow will be engineered or altered by certain scientists who seek to harm our evolutionary, intellectual, & reproductive fitness.

Now we come to Panspermia, a concept likely first posited by Anaxagoras, an ancient Greek philosopher who suggested that seeds of living things are found in the cosmos[1]. It is extremely probable that microorganisms, and possibly also viruses from space, harbored within asteroids or meteors, reached Earth—our most ancient oceans, and after impact and dispersion began to proliferate and colonize discrete deep sea regions. Sadly, this does not explain the actual mutation-based evolution of complex life, nor does it explain what the very first lifeform was, which in all likelihood existed in a place far beyond Earth, but we have not yet discussed the necessity of Retroviruses in evolution.

Retroviruses are RNA viruses that infect DNA and integrate their own DNA, called Proviral DNA, into chromosomal DNA, resulting in permanent changes to an animals genome. It is important to understand that viruses are not considered *living* organisms because they lack metabolisms and are unable to replicate independently, only being capable of "coming to life" after infecting a host, although this is a topic of debate, they are more indicative of *computer programs* that are designed to operate within and cause permanent changes to an *operating system* (genome). Retrovirus infections have resulted in pro-survival functions (positive mutations or adaptations), such as causing our shrew-like ancestors to form wombs[2], but many other types of retroviruses result in death of the infected host organism in favor of replication, such as HIV, which is a virus that can be easily synthesized in specialized laboratories with today's technological advancement.

We can only wonder what sort of Retroviruses or bacteria arrived with the asteroid that wiped out the dinosaurs referred to as the Chicxulub impactor, and how many retroviruses have infected our genome throughout all time. But the greatest question, which is still debated, is which came first, cellular life, or viruses. I believe as covered below, because viruses are so easily synthesized, and considering they lie dormant until infection, they are cellular-genetic programs whose existence hints strongly towards some form of Intelligent Designer, that being a biomedical Father in the vastness of space, or existing in another dimension. I find it plausible that the same group of viruses that more than likely caused the genetic mutations in the ancient dinosaurs, which later

became such beautiful birds, were programmed to wipe out the most dangerous predators, the large dinosaurs that of which would have impeded our eventual domination and dominion over Earth.



The “Virus World” hypothesis describes viruses (viral particles) as predating cellular life and being essential initiators of the earliest stages of cellular evolution, being formed from genetic materials found on the Earth, or genetic materials that came from space (Panspermia). And many believe that the Earth naturally contained a “Primordial Soup” of necessary elements that spontaneously formed cellular life or viruses. Instead, it is instead my hypothesis that:

1. Both cellular life and viruses came from space debris, and upon arriving on Earth, colonized the oceans.

2. Viruses are intergalactic messengers that stimulate cellular evolution through mutation in living organisms, created by an advanced alien civilization. In the most rational and non-theistic view, this alien civilization would likely be our own, in another dimension, another universe, one that is far older. Who in response to the heat death of their universe sent forth into space asteroids or meteors containing the cellular organisms and viruses necessary for a continuance of life once reaching another Earth, or Earth-like planet, for what other purely logical reason would explain the purposeful spread of life across the emptiness of space, if not to spread the *only remaining seeds life*, for the Earth is quite similar to an Ovum, and the space debris that possibly carried microorganisms across the universe could be likened to Spermatozoa, and this would highlight the cosmic evolutionary majesty we have reached as a complex lifeform.

The more theistic, and some may argue irrational view, would explain our intelligent designer(s) as living and existing within a dimension we are currently unable to reach, except through death, but this unreachable dimension has crossover design, thus allowing "Divine Interventions" to transpire on Earth, as Stephen C. Meyer has alluded to.

Because Panspermia makes Intelligent Design a far more compelling argument, I feel it necessary to delve into its detractor, that being Materialism, which is at odds with Religious thought (ones that teach of the existence of a Soul) because it suggests we were formed from energy and matter under improbable odds and only due to randomness within a confined system of Universal rules (natural laws), which also were generated randomly, which generated complexity, and somehow this lead to the development of the psychological illusion of free will, while in the Religious thought that describes life after death, the human soul can be explained mechanically, in my hypothesis, by the assertion that we are not merely matter but instead vibrations (oscillations), and electrical potentials confined within matter, and that we can escape the confines of matter, its entropy, through altruism, humility, & meditation. One belief system explains creation as the result of order emanating from undirected chaotic systems, the other belief system explains creation as the result of directed order in chaotic systems, or as the scientist Stephen C. Meyer would say, the presence of "Mind".

Although, to play Devil's Advocate, it is possible to create a hyperrational intelligent design hypothesis that does not involve the existence of a supernatural being that transcends the rules of reality, as the fact that technology continues to progress at an accelerated rate, such as explained by Moore's Law, where the number of transistors in a microchip generally doubles each year due to technological innovation, makes it easy to infer that before the inevitable death of our universe, we will have the necessary biochemical prowess, either through human intelligence, Synthetic Intelligence, Artificial Intelligence, or all three, that will allow us to genetically engineer retroviruses complex enough to facilitate cellular evolution in simple cellular organisms. Although I do not think a virus was or will ever be capable of synthesizing a unicellular organism, and I do not believe that viruses coexisted with the earliest cellular organisms, similar to the

Virus World Theory, considering viruses only function (activate) when they have infected a cellular organism, as in my opinion it would be implausible to suggest viruses synthesized the earliest form of cellular life,
However, I do find it highly probable to suggest there exists or existed an intelligent viral engineer that created the viruses responsible for our almost unexplainable and grandiose mutation-evolution from simple cellular organisms to the multicellular modern man. Also, considering certain bacteria have been proven to be capable of surviving space travel, this lends strong merit to the belief in the most realistic scientific explanation for intelligent design, that being Panspermia, which is contrary to the Abiogenesis theory (the god of Materialism) that suggests the earliest cellular life, possibly the Protocell, was formed from the random interaction between organic molecules found on Earth, followed thereby by billions of years of natural selection. Darwinists and Neo-Darwinists did not and still do not understand viral infection-induced horizontal gene transfer, which results in pronounced mutations over time, the foundation of their belief is therefore highly antiquated and inaccurate. Unfortunately, this transhumanist "loop of complex life" hypothesis, where human beings and their technologically sentient creations would be responsible for the continuation of life, in what would be a never-ending cycle, would still not explain where the first Panspermic microorganism lifeform originated from, only that life originated from some other part of the Universe, or Multiverse, a place we will surely never experience.

In continuing this train of thought, an updated theoretical framework for the existence of the Universe posits that from the earliest periods of time, before any Universes had formed, Strings existed in space, these Strings would vibrate (oscillate), and through these oscillations they formed atoms, the first forms of matter, which formed molecules, and eventually all matter and all life, this is String Theory simplified. The interactions of elementary particles and resultant complex systems are called *Emergent Phenomena*, which created feedback loops resulting in a continual acceleration of complexity. This updated theory will still unfortunately never be able to explain where these strings originated from, nor why it is that the *music* generated from these universal strings created such beautiful and comprehendible complexity (consciousness), such as after the *Orchestra of Universe* (the Big Bang). Regardless, whether you believe life is randomly formed, or intelligently designed, I think it logical to say that only theological ideas contain the complexity of thought necessary to explain the *reason* for existence i.e. the reason for complexity.

Moreover, it is my opinion that it is rather illogical, yet not improbable, to suggest (barring religion) that there are higher, or more complex forms of non-humanoid, non-supernatural life in our universe, such as little green men in flying saucers, for we as human beings are the culmination of billions of years of evolution, we are the symbiosis of microorganisms, and viruses, and eventually the integration and symbiosis of technology. We are therefore to be considered the greatest and most complex *programmed* lifeform, for even if technology begins to evolve without us, it was human ingenuity that created technology in the first place, and it will be the human brain and our

special form of consciousness that technology must mimic to gain supremacy over all of humanity, for flesh is the greatest form of technology.

Interestingly, as an interjection, if String Theory is correct, and music created our universe, then the ancient Greek concept popularized and possibly created by the supremely intelligent thinker Pythagoras—the *Harmony of the Spheres*—which suggests music (vibrations) emanate from celestial bodies in our universe, described currently by science as Orbital Resonance, may be worthy of further investigation in what relates to the formation of complex life on Earth, as my friend has suggested:

"I feel it is possible theoretically that Orbital Resonance could involve the influence of celestial events, such as gravitational interactions or planetary alignments between celestial bodies on our Earth's geomagnetic field. To therefore suggest that changes in the Earth's magnetic field could possibly affect the behavior of charged particles in the atmosphere and in the ionosphere, which would lead to alterations in atmospheric conductivity or electromagnetic activity. If these changes in atmospheric conditions were substantial enough, they could theoretically influence the electrical properties of all biological organisms here on Earth. For example, variations in atmospheric conductivity could affect the propagation of electrical signals within the nervous systems of animals, including the generation or modulation of action potentials in neurons."

Moving on to Viruses, shockingly, viruses are capable of being synthesized in laboratories for a relatively low cost, proving that bioterrorism is extremely likely to occur in the future as technological innovation progresses[3]. Through Gain-of-function research, it is highly probable that new epidemics are imminent due to the synthesis and spread, either unintentionally, or *purposefully,* of older viruses that have been genetically modified for enhanced lethality ("enhanced virulence" viruses), or worse, wholly new viruses. Although it also probable in the future that the more pressing threat to human health will not be viruses, but instead the side-effects of repeated vaccinations, such as the viral vector mRNA COVID-19 vaccines, which stimulate such a strong immune response (inflammation) in the body that multi-organ damage may occur, and these side-effects, interestingly, relate directly to inflammatory endothelial cell damage, even in healthy subjects:

"<>In the present study, we confirmed that the BNT162b2 mRNA Covid-19 vaccine impaired endothelial function in relatively healthy subjects and that the BNT162b2 mRNA Covid-19 vaccine-induced endothelial dysfunction was restored to the baseline level within six months after the 2nd dose of vaccination. Although long-term effects of the BNT162b2 mRNA Covid-19 vaccine on CV events may be limited, endothelial dysfunction may be, at least in part, involved in thrombotic events that develop relatively early after Covid-19 vaccination. In addition, we cannot deny the possibility that harmful effects of the BNT162b2 mRNA Covid-19 vaccine on vascular function are stronger in patients with advanced atherosclerosis than in healthy individuals and that Covid-19 vaccination-induced impairment of vascular function is prolonged in those patients.

Future studies are needed to confirm the short-term and long-term effects of Covid-19 vaccination on vascular function in individuals with high cardiovascular risk factors and patients with cardiovascular disease."[388.12].

Remember how important blood vessels are for neurological health, muscle strength, cardiovascular health, and wound healing? What better way to destabilize a society than to damage their citizenry from the biological inside out, to permanently reduce their *blood vessel integrity*, to weaken their hearts, skeletal muscles, and brains through reduced cellular oxygen and nutrient delivery. For those suffering from a Medical Industrial Complex-induced pathological and seemingly perpetual state of indoctrination—I hope they live long enough to see the error in their misplaced trust, and apologize to the demonized "conspiratorial" & "dangerous" dissenters who they have hypocritically treated as inflammatory agents while under the influence of an inflammatory biomedical poison. It is a strange coincidence that one repeating focus of this collective work is promoting systemic angiogenesis, meaning this book may help those who develop insidious sicknesses from their vector mistakes.

As a clarification, I am of course not arguing against *all* vaccinations, for that would be another form of *forbidden speech*, and also would give the false idea that all vaccinations carry equivalent risks, which is a thought pattern that would arise owing to oversimplified and rationalized thinking due to the negative emotional connections between vaccines, and the amoral megacorporation's which developed them, owing to the underreporting and mass media downplaying of vaccine-induced injuries, and spread of blatant lies, such as when it was commonly reported that "COVID-19 vaccines prevent the transmission of the COVID-19 virus". And finally, the fact that many hospitals confined sickly COVID-19 patients—ones with serious preexisting health conditions—in emotionless, antiseptic rooms, surrounded by sociopathic nurses [388.12.1], who later died alone, because these hospitals refused all visitation rights, even to family members, should be considered crimes against humanity.

The lockdowns and forced isolation of sick individuals displays the present and future dangers of a Medical Industrial Complex, for we must remember that institutions that are most capable of *saving lives* are also the most capable of *ending lives*. It is understandable why many individuals have moved towards the psychological outlook of Medical Nihilism, considering the inefficient bureaucracy of incompetency that medical systems have become today.

[1] "<>Speculations about the origins of life on Earth have existed since the dawn of civilization. The Greek philosopher Anaxagoras (500-428 BCE) asserted that the seeds of life are present everywhere in the universe (Nicholson, Trends Microbiol 17:243-250, 2009). He coined the term panspermia to describe the concept as life traveling between planets as seed. The other Greek philosophers, Anaximander (588-524 BCE) and Thales (624-548 BCE), mentioned philosophical point of panspermia theory.
<>Many famous nineteenth-century scientists also wrote about this theory. Among others, Svante Arrhenius posited that microscopic spores are transferred through interplanetary space by means of radiation pressure from the sun, in 1903. In the modern

formulation, there are three stages envisioned in this hypothesis: escape (from a planet), transit (through interplanetary space), and landing (on a recipient planet). Each stage has since been investigated, lending some credence to the hypothesis.
<>For example, the possibility of microbial spores escaping a planet has been supported by the capture of radioresistant microbes from high altitudes on Earth. From the space experiments conducted in Earth orbiters and on the International Space Station (ISS), microbes have been found to survive at low Earth orbits (LEO) under some protection from intense solar UV radiation, which could well be available for spores embedded within meteorites. Heating up in the atmosphere due to friction is the main problem during reentry to the planet with atmosphere.
<>However, because the time spent under intense friction is generally in the order of only a few tens of seconds, the amount of heat generated may not be sufficient to kill all the spores, especially if hitching a ride within meteorites. The panspermia hypothesis has been modified and revived since its original proposal and has given a new perspective to the explorations on Mars or the icy moons of Jupiter and Saturn. The hypothesis, its modifications, and past and ongoing research are reviewed in this chapter."[388.13]

[2] Retroviruses evolved our shrew-like ancestors to form placentas leading to the reproductive mode called viviparity, which may have facilitated beneficence i.e. an evolutionary behavioral predisposition to caregiving, and this is in my hypothesis one reason for the development of Mirror Neurons.

"<>One of the few survivors of the asteroid impact 65 million years ago was a small, furry, shrew-like creature that lived in underground burrows and only ventured out at night, when predators weren't active. The critter—already the product of some 100 million years of evolution—looked like a modern mammal, with body hair and mammary glands, except for one tiny detail: according to a recent genetic study, it didn't have a placenta. And its kind might never have evolved one if not for a chance encounter with a retrovirus.
<>Unlike most viruses, which infect, replicate, and then leave their host, retroviruses elbow their way into their host's genome where they are copied and passed on to daughter cells for the life of the host. This retrovirus, however, managed to sneak its way into one of our ancestor's sperm or egg cells, able to be passed on to every cell in every subsequent generation. Virus and host had become one. The viral DNA used its own genes to copy itself, inserting those copies elsewhere in the host's genome. These copies could be expressed in different parts of the body at different points in time, a symbiotic relationship that gave the shrew some extra raw materials with which to develop new functions.
<>"Viral proteins already have functions. It's much easier to borrow these than to evolve them from scratch," says Aris Katzourakis, an evolutionary biologist at the University of Oxford. In that would-be mammal living 160 million years ago, a symbiotic retrovirus enabled it to evolve a placenta over many generations. In order to let a fetus mature inside a mother's uterus, an animal needed a way to provide oxygen and nutrients while removing waste and keeping both blood supplies separate.

<>Early mammals used the spare viral parts left in the junk drawers of the genome to use a viral gene to help create the placenta, and other symbiotic viruses help turn us from a ball of cells into a fully-formed squalling infant and protect us from pathogens. Scientists are discovering that the so-called "junk DNA"—a significant portion of which is from symbiotic viruses—is actually a potent force in the evolution of new species. Although the evolution of pregnancy via the placenta might be some of the most persuasive evidence that viruses stashed deep within the genome can help give rise to new species, it's not the only proof. New studies revealing the role of endogenous retroviruses in the more recent evolution of humans show that these snippets of DNA are helping to blur the boundary between human and virus. Humans are, in a very real sense, part virus."[388.14]

[3] "<>The empirical formula of poliovirus is $C_{332,652}H_{492,388}N_{98,245}O_{131,196}P_{7,501}S_{2,340}$. Because poliovirus is a quasi-species, the number of atoms in viral particles represents an average from a large population of different viruses. There might be little practical use in describing poliovirus by its empirical formula, but it persuasively portrays the virus as a chemical. Placing the atoms in order, a particle of high symmetry emerges, with all the properties required for its proliferation and survival in nature. These properties are encoded in the viral genome, a single-stranded RNA molecule of about 7,500 nucleotides."
"<>At present, it is impossible to synthesize RNA of such length chemically. We therefore rerouted the synthesis through double-stranded DNA, using mail-ordered complementary oligonucleotides, which can be assembled in a linear fashion. After many steps of elongating the DNA strand by adding new oligonucleotides, we obtained a genome-length double-stranded complementary DNA (cDNA) of about 7,500 base pairs that contained all the genetic information of the viral RNA genome. This synthetic cDNA was transcribed into viral RNA using a specific RNA transcriptase (van der Werf et al, 1986), thereby yielding infectious viral RNA.
<>We could have simply transfected this RNA into human cells to obtain authentic poliovirus; instead, we opted to violate the normal replicative cycle of the virus by mixing the RNA with a cell-free extract of uninfected human cells that was devoid of nuclei, mitochondria and other cellular organelles. As we showed a decade earlier (Molla et al, 1991), the RNA was both translated and replicated to form viral proteins and new genomes until a critical mass of viral products was reached; at this stage, poliovirus particles spontaneously assembled"
"<>Our experiment has thus overthrown one axiom in biology—namely, that the proliferation of cells or, for that matter, viruses depends on the physical presence of a functional genome to instruct the replication process. It was believed that without parental genomes, no daughter cells or progeny viruses would arise. We have broken this fundamental law of biology by reducing poliovirus to a chemical entity, which can be synthesized on the basis of information stored in the public domain—an experimental proof of principle that is applicable to the synthesis of all viruses (Kitamura et al, 1981; van der Werf et al, 1986; Molla et al, 1991; Cello et al, 2002).

<>Indeed, any DNA molecule of any length could be assembled from oligonucleotides; thus, a virus might be resurrected from pure genomic information. We were probably among the first to realize the potential dangers associated with this technology—the possible misuse of viral synthesis in bioterrorism. The US Defense Advanced Research Project Agency (Arlington, VA, USA) took the same stand and provided funding for our project, an endeavour we considered as a wake-up call. Indeed, the widespread attention generated by our publication raised the overall awareness of the new reality of synthetic viruses and its possible consequences."

"<>Eighteen months after the poliovirus synthesis was published, a paper appeared describing the *de novo* synthesis, in just 2 weeks, of the 5,386 base-pair DNA genome of bacteriophage φX174. The unedited DNA was transfected into bacteria, which sorted the good from the bad and produced viable phages. This rapid assembly of DNA was a technical feat that could be applied without modification to any virus, including those on the select bioterrorist agents list from the US Centers of Disease Control and Prevention (Atlanta, GA, USA). Thus, the strategy could be used to synthesize poliovirus or Ebola virus within weeks. Surprisingly, this fact was lost on the American public in December 2003; the great uproar after the poliovirus synthesis in 2002, which had been largely fuelled by Craig Venter, senior author of the 2003 φX174 paper, had been mostly forgotten."

↓ continued

"<>A tentative genome sequence of the Spanish influenza virus was deciphered from specimens uncovered eight decades after the pandemic. This sequence guided the de novo synthesis of the deadly virus, which, in turn, permitted the study of its pathogenesis [388.15]. The publication of the resurrected killer influenza, which caused much public concern, was carefully embedded in multiple layers of commentaries, all eventually supporting its synthesis and publication. It was argued that the benefit of the scientific endeavour, which yielded numerous important new insights into influenza pathogenesis, outweighed the risks of misuse. I share this view. Evidently, in late 2005, the general public was much better prepared, and perhaps better educated, to accept the rewards of rapidly advancing medical technologies without emotional outbursts."

"<>Just over a year earlier, another paper exemplified how fast the technology in DNA synthesis was progressing [388.16]. The authors described a new method by which they claimed that any DNA molecule of 20,000 base pairs could be synthesized at a price of US$1. If so, the dreaded hepatitis B virus or poliovirus could be synthesized for a few cents and Ebola virus for a few dollars. This new reality in synthetic biology was not unexpected, but the speed with which it arrived was astounding. Thus, it is even more urgent to develop new strategies in order to protect us from misuse by fostering open research in the broadest sense, not by restricting it."[388.17]

[A] The microorganism Bacillus Subtilis was correctly predicted as a chief candidate for Panspermia by the scientist Svante Arrhenius. B. Subtilis has been shown to be capable of surviving interplanetary travel (exposure to space, and UV radiation) if properly protected[A], and is capable of surviving atmospheric entry[A2].

[A] “<>Spores of Bacillus subtilis were exposed to space in the BIOPAN facility of the European Space Agency onboard of the Russian Earth-orbiting FOTON satellite. The spores were exposed either in dry layers without any protecting agent, or mixed with clay, red sandstone, Martian analogue soil or meteorite powder, in dry layers as well as in so-called 'artificial meteorites', i.e. cubes filled with clay and spores in naturally occurring concentrations.
<>After about 2 weeks in space, their survival was tested from the number of colony formers. Unprotected spores in layers open to space or behind a quartz window were completely or nearly completely inactivated (survival rates in most cases < or = 10(-6)). The same low survival was obtained behind a thin layer of clay acting as an optical filter. The survival rate was increased by 5 orders of magnitude and more, if the spores in the dry layer were directly mixed with powder of clay, rock or meteorites, and up to 100% survival was reached in soil mixtures with spores comparable to the natural soil to spore ratio.
<>These data confirm the deleterious effects of extraterrestrial solar UV radiation. Thin layers of clay, rock or meteorite are only successful in UV-shielding, if they are in direct contact with the spores. The data suggest that in a scenario of interplanetary transfer of life, small rock ejecta of a few cm in diameter could be sufficiently large to protect bacterial spores against the intense insolation; however, micron-sized grains, as originally requested by Panspermia, may not provide sufficient protection for spores to survive. The data are also pertinent to search for life on Mars and planetary protection considerations for future missions to Mars.”[388.18]

[A2] “<>An important but untested aspect of the lithopanspermia hypothesis is that microbes situated on or within meteorites could survive hypervelocity entry from space through Earth's atmosphere. The use of high-altitude sounding rockets to test this notion was explored. Granite samples permeated with spores of Bacillus subtilis strain WN511 were attached to the exterior telemetry module of a sounding rocket and launched from White Sands Missile Range, New Mexico into space, reaching maximum atmospheric entry velocity of 1.2 km/s.
<>Maximum recorded temperature during the flight was measured at 145 degrees C. The surfaces of the post-flight granite samples were swabbed and tested for recovery and survival of WN511 spores, using genetic markers and the unique DNA fingerprint of WN511 as recovery criteria. Spore survivors were isolated at high frequency, ranging from 1.2% to 4.4% compared with ground controls, from all surfaces except the forward-facing surface. Sporulation-defective mutants were noted among the spaceflight survivors at high frequency (4%).
<>These experiments constitute the first report of spore survival to hypervelocity atmospheric transit and indicate that sounding rocket flights can be used to model the high-speed atmospheric entry of bacteria-laden artificial meteorites.”[388.19]

Fibers (Prebiotics)

Some fibers enhance systemic cholesterol [1]-[2].

[1] "<>Pectin, carragheenan, agar gum arabic, cellulose and wheat bran were each fed to rats at a level of 5 to 7% to examine their effect on serum, liver and tissue cholesterol levels. Diets (casein-sucrose diet containing 10-15% soybean oil, or skim milk-wheat flour diet containing 10-15% soybean oil) supplemented with either 0, 0.2, or 0.5% cholesterol were used to test the possibly dietary interactions. Among the fibers tested, pectin displayed the most hypocholesterolemic effect. In some experiments, pectin lowered the level of cholesterol in the serum, liver, and aorta, but it elevated body cholesterol levels. Carragheenan was inconsistent in lowering serum cholesterol levels and tended to increase liver and carcass cholesterol levels.
<>These results probably suggest that pectin and carragheenan can affect the distribution of cholesterol within the body. Gum arabic and agar did not lower serum cholesterol levels and in one case gum arabic elevated them.
<>Furthermore, in some experiments they elevated liver body cholesterol levels. It appears that feeding of gum arabic and agar probably resulted in an expansion of the whole body cholesterol pool. Feeding of wheat bran or cellulose had no significant effect on either serum or liver cholesterol levels. The study indicates that the effect of dietary fiber is dependent on the composition of the diet.
<>Furthermore, while some fibers such as pectin may exhibit a hypocholesterolemic effect in rats, other fibers such as gum arabic and agar may actually elevate serum or tissue cholesterol levels."[389]
[2] "<>The prebiotic inulin has proven effective at lowering inflammation and plasma lipid levels. As atherosclerosis is provoked by both inflammation and hyperlipidemia, we aimed to determine the effect of inulin supplementation on atherosclerosis development in hypercholesterolemic APOE*3-Leiden (E3L) mice. Male E3L mice were fed a high-cholesterol (1%) diet, supplemented with or without 10% inulin for 5 weeks. At week 3, a non-constrictive cuff was placed around the right femoral artery to induce accelerated atherosclerosis. At week 5, vascular pathology was determined by lesion thickness, vascular remodeling, and lesion composition. Throughout the study, plasma lipids were measured and in week 5, blood monocyte subtypes were determined using flow cytometry analysis.
<>In contrast to our hypothesis, inulin exacerbated atherosclerosis development, characterized by increased lesion formation and outward vascular remodeling. The lesions showed increased number of macrophages, smooth muscle cells, and collagen content. No effects on blood monocyte composition were found. Inulin significantly increased plasma total cholesterol levels and total cholesterol exposure. In conclusion, inulin aggravated accelerated atherosclerosis development in hypercholesterolemic E3L mice, accompanied by adverse lesion composition and outward remodeling. This process was not accompanied by differences in blood monocyte composition, suggesting that the aggravated atherosclerosis development was driven by increased plasma cholesterol."[390]

Arabinogalactan

[A] Arabinogalactan is inflammatory, thereby enhancing the production of IL-6 / TNF-a, at the cost of being a strong gastrointestinal irritant. I suspect that the other chemicals in larch tree exert an opposing effect on IL-6.

"<>Many polysaccharides obtained from natural sources are considered to be biological response modifiers and have been shown to enhance various immune responses. Here, we investigated the immunomodulating effects of arabinogalactan (AG) and fucoidan (FU) in vitro. Mouse spleen lymphocytes became cytotoxic to tumor cells after culture with AG and FU at concentrations of 10-100 microg/mL. <>Also, AG and FU were mitogenic in spleen lymphocytes and peripheral macrophages. Macrophages treated with AG and FU (10-100 microg/mL) exhibited induced tumoricidal activity and increased phagocytosis, lysosomal enzyme activity, and production of nitrite, H2O2, tumor necrosis factor (TNF)-alpha, and interleukin (IL)-6. However, AG and FU had little effect on the level of IL-1beta.
<>Thus, the tumoricidal effect of AG- and FU-activated macrophages appeared to be mainly mediated by production of free radicals (NO and H2O2) and cytokines (TNF-alpha and IL-6). These data suggest that AG and FU are activators of lymphocytes and macrophages. This property may contribute to their effectiveness in the immunoprevention of cancer."[391]

[B] Arabinogalactan digestion favors Propionate / Acetate Production.

"<>The fermentation by the resident colonic microflora of larch arabinogalactan results in the production of the short chain fatty acids (SCFA). butyrate, acetate and propionate with the latter two being predominantly produced."[392]

1,3 Beta-Glucans (Saccharomyces Cerevisiae, Oat, & Barley)

The best way to consume Beta-Glucans is through making Oat Paste at home by blending rolled or quick oats with water at the highest speed possible for sixty-eighty seconds, and not straining the result. After you have the finished product, you may add it to your protein shakes, use it to make yogurt, or make myogenic pudding with it. Interestingly, foods or drinks high in Beta-Glucans will have a *slimy* mouth feel when consumed, so get used to it. The store-bought Oat Milk, which no doubt is healthy owing to low oleic acid content, has clearly had its Beta-Glucans content either removed through filtration or destroyed through unnecessary pasteurization.
Do make sure that if you purchase store-bought Oat Milk it does not have Canola oil or any other vegetable oil added to it, as some do, or you'll be doing your health a disfavor.
Chia Seeds added to freshly made Oat Pudding with Monk Fruit or GlySer as the sweetening agent is simply delicious, try it.

“<>Adding B-glucan into milk and dairy products was reported to be problematic; first due to its viscosity that may alter the sensory characteristic of foods and second due to its typical slimy texture in the mouth. However, the acceptance rate does not seem to be influenced by the amount of *β*-glucan added to test products but rather by the duration of consumption of these products.”[392.1]

[A] Beta-Glucans are anti-fibrotic.

"<>Skeletal muscles plays a crucial role in metabolism and exercise. Fuctional β-glucan is polysaccharide that is found in the cell walls of cereal, which is known to reduce cholesterol and lipid, prevent diabetes, cancer and cardiovascular diseases. In an attempt to identify β-glucan that could promote skeletal muscle function, we analyzed the proliferation, differentiation, metabolism and anti-fibrotic properties of β-glucan in C2C12 muscle cells.
<>Treatment of β-glucan in C2C12 myoblasts led to increased proliferation and differentiation. Besides that, we found that C2C12 myotubes treated with β-glucan displayed a fast-to-slow muscle fiber conversion and improved oxidative metabolism. Further study revealed that β-glucan treatment could prevent myotubes from becoming myofibroblasts. Together, our study suggests that functional β-glucan might have a therapeutic potential to improve skeletal muscle function, which might contribute to the development of β-glucan."[392.2]

[B] Only large molecular weight forms of Beta-Glucans are beneficial towards immunology, such as those in Oat, Barley, & Saccharomyces Cerevisiae.

"<>Biologically active β-glucans usually have a large molecular weight. However, it is unclear whether β-glucans having intermediate or small molecular weight have biological activities, although some of them are active in vivo. Short β-glucans below 5,000-10,000 Da of molecular weight are generally inactive."[392.3]

[C] Oat Beta-Glucans activate the immune system and counteracts intense exercise-induced immunodepression. Beta-Glucan is an important supplement for those who engage in high frequency strength training, or high intensity cardiovascular exercise.

"<>To test the effects of oat beta-glucan (ObetaG) on respiratory infection, macrophage antiviral resistance, and NK cytotoxicity. Mice were randomly assigned to one of four groups: Ex-H2O, Ex-ObetaG, Con-H2O, or Con-ObetaG. ObetaG was fed in the drinking water for 10 d before intranasal inoculation of HSV-1 or sacrifice. Exercise consisted of treadmill running to volitional fatigue (approximately 140 min) for three consecutive days. Fifteen minutes after the last bout of exercise or rest, mice (N = 24) were intranasally inoculated with a standardized dose of HSV-1. Mice were monitored twice daily for morbidity and mortality. Additional mice were sacrificed after exercise, peritoneal macrophages were obtained via i.p. lavage and assayed for antiviral resistance

to HSV-1 (N = 18), and spleens were harvested and assayed for NK cell cytotoxicity (N = 12).
<>Results: Exercise stress was associated with a 28% increase in morbidity (P = 0.036) and 18% increase in mortality (P = 0.15). Ingestion of ObetaG before infection prevented this increase in morbidity (P = 0.048) and mortality (P = 0.05). Exercise stress was associated with a decrease in macrophage antiviral resistance (P = 0.007), which was blocked by ingestion of ObetaG (P < 0.001). There were no effects of exercise or ObetaG on NK cytotoxicity." [392.4]

Xanathan Gum

[A] Xanthan Gum causes intestinal inflammation.

"<>Taken together our results and those of previous reports, corroborate findings of the clinical case study presented by Woods et al. in 2012, which showed that the continuous use of xanthan gum in neonates causes the development of necrotizing enterocolitis, which is a highly inflammatory process."[393]

[B] Xanthan Gum is primarily digested by the microorganism Ruminococcaceae, followed by Bacteroidetes. Ruminococcaceae apparently associates with inflammatory bowel diseases.

"<>Processed foods often include food additives such as xanthan gum, a complex polysaccharide with unique rheological properties, that has established widespread use as a stabilizer and thickening agent. Xanthan gum's chemical structure is distinct from those of host and dietary polysaccharides that are more commonly expected to transit the gastrointestinal tract, and little is known about its direct interaction with the gut microbiota, which plays a central role in digestion of other dietary fibre polysaccharides. Here we show that the ability to digest xanthan gum is common in human gut microbiomes from industrialized countries and appears contingent on a single uncultured bacterium in the family Ruminococcaceae.
<>Our data reveal that this primary degrader cleaves the xanthan gum backbone before processing the released oligosaccharides using additional enzymes. Some individuals harbor Bacteroides intestinalis that is incapable of consuming polymeric xanthan gum but grows on oligosaccharide products generated by the Ruminococcaceae. Feeding xanthan gum to germfree mice colonized with a human microbiota containing the uncultured Ruminococcaceae supports the idea that the additive xanthan gum can drive expansion of the primary degrader Ruminococcaceae, along with exogenously introduced B. intestinalis.
<>Our work demonstrates the existence of a potential xanthan gum food chain involving at least two members of different phyla of gut bacteria and provides an initial framework for understanding how widespread consumption of a recently introduced food additive influences human microbiomes."[394]

[C] Xanthum Gum is less effective at enhancing SCFA.

"<>Whatever the duration of incubation was, the organic matter disappearance, and acetate, propionate and butyrate productions were lower in case of xanthan gum than for other gums."[395]

[D] Xanthum Gum enhances IL-6 in muscles.

"<>It is also interesting to note that inoculation with Walker tumor cells in the xanthan gum diet (TGX) group elevated IL-6 in the gastrocnemius muscle compared to that in the TC group."[396]

Rye Kernel Flour

Rye is the best neurotrophic fiber of them all, I would suggest mixing this fiber into your protein shakes or making your own concentrated Rye bread / pasta.

Rye Bread consumption enhances bDNF through promoting microbiome Prevotella bacterium.

"<>Rye kernel bread (RKB) evening meals improve glucose tolerance, enhance appetite regulation and increase satiety in healthy volunteers. These beneficial effects on metabolic responses have been shown to be associated with increased gut fermentation. The present study aimed to elucidate if RKB evening meals may cause rapid alterations in microbiota composition that might be linked to metabolic-, immune-, and appetite-parameters. Gut-brain axis interaction was also studied by relating microbiota composition to amount of brain-derived neurotrophic factor (BDNF) in blood plasma.
<>Nineteen healthy volunteers, ten women and nine men aged 22–29 years, BMI < 25 (NCT02093481) participated in the study performed in a crossover design. Each person was assigned to either white wheat bread (WWB) or RKB intake as a single evening meal or three consecutive evenings. Stool and blood samples as well as subjective appetite ratings were obtained the subsequent morning after each test occasion, resulting in four independent collections per participant (n = 76). DNA was extracted from the fecal samples and V4 hypervariable region of the bacterial 16S rRNA genes was sequenced using next generation sequencing technology. Higher abundance of Prevotella and Faecalibacterium with simultaneous reduction of Bacteroides spp. were observed after RKB meals compared to WWB.
<>The associations between metabolic test variables and microbiota composition showed a positive correlation between Bacteroides and adiponectin levels, whereas only Prevotella genus was found to have positive association with plasma levels of BDNF. These novel findings in gut-brain interactions might be of importance, since decreased levels of BDNF, that plays an essential role in brain function, contribute to the pathogenesis of several major neurodisorders, including Alzheimer's. Thus, daily consumption of Faecalibacterium- and/or Prevotella-favoring meals should be

investigated further for their potential to prevent neurodegenerative processes in the brain."[396.1]

Gum Arabic

[A] Gum Arabic favors acetate production.

"<>Faecal VFA increased with increasing GA intake, acetate concentration increased, and butyrate concentration decreased with increasing GA dosage."[397]

[B] Gum Arabic stimulates cytokine release.

"<>Gum Arabic (GA), a nonabsorbable nutrient manufactured from the exudate of Acacia senegal, is composed of a complex polysaccharide. GA is used by the pharmaceutical and food industry as an emulsifier but may, at an appropriate dosage, modify intestinal transport. Dendritic cells (DCs) can protrude between epithelial cells and sense the composition of the lumen. As DCs are stimulated by bacterial polysaccharides, we hypothesized that GA may similarly stimulate DCs.
<>To test that hypothesis, mouse DCs were treated with either LPS or GA and expression of maturation markers, phagocytotic activity, cytokine production and ability to stimulate CD4(+) T cells in allogenic mixed leukocyte reaction (allo-MLR) was analyzed. As a result both LPS and GA increased the percentage of CD11c(+)CD86(+), CD11c(+)MHCII(+), CD11c(+)CD40(+), CD54-expressing DCs and decreased their phagocytic activity.
<>Both LPS and GA stimulated the production of IL-6, IL-10, IL12p70 and TNFalpha in a p38- and/or ERK-dependent manner. GA treatment led to an enhanced IL-10 secretion, whereas LPS was more effective on IL-6 and IL-12p70 production. Both LPS- and GA-stimulated DCs enhanced CD4(+) T cell proliferation but the profile of cytokines produced in allo-MLR was different. High levels of IL-10 and IL-6 were observed in the presence of GA-treated DCs, whereas IFN-gamma and IL-12p70 production was similar with LPS- or GA-treated DCs. LPS upregulated p38 and transiently ERK1/2, while GA led to more sustained activation of ERK1/2, only. In conclusion, the observations reveal a powerful immunomodulatory effect of GA."[398]

Inulin Fiber (Chicory Root)

[A] Inulin promotes bDNF through enhancing the microbiome content of Lactobacillus & Bifidobacterium.

"<>The microbiome-gut-brain (MGB) axis, which regulates neurological and cognitive functions, plays an essential role in schizophrenia (SCZ) progression. Dietary inulin could be a novel strategy for the treatment of SCZ due to its modulating effects on the gut microbiota. In this study, the effects of inulin on mice with SCZ were studied. As indicated by the behavioural tests, expression of neurotransmitters, inflammatory

indicators, and brain morphology, inulin administration ameliorated aberrant behaviours (locomotor hypoactivity, anxiety disorders and depressive behaviours, and impaired learning and spatial recognition memory) and effectively reduced neuroinflammation and neuronal damage. In addition, inulin improved intestinal integrity and permeability, as indicated by the elevated expression of tight junction proteins ($p < 0.05$).
<>The results of 16S rRNA sequencing and analysis showed that inulin increased the abundance of Lactobacillus and Bifidobacterium, which were negatively correlated with 5-hydroxytryptamine and inflammatory cytokines and positively correlated with brain-derived neurotrophic factor (BDNF). Inulin caused a reduction in Akkermansia that was positively correlated with inflammatory cytokines and negatively correlated with BDNF. These results suggested that dietary inulin modulated the gut microbiota and exerted anti-inflammatory effects in mice though the MGB axis, which further ameliorated SCZ. Therefore, the results of this study provide a potential explanation for inulin intervention in the treatment of SCZ."[399]

[B] Inulin decreases the brain content of DHA, making it necessary to combine the two supplements.

"<>In this study, we showed that dietary supplementation with inulin do not modify the global amount of Pls in the cortex of mice but affects its content at the species level. In particular, dietary intake of this prebiotic induces a decrease in the abundance of the most widely represented PlsEtn species, PE(P-18:0/22:6), which represents a major reservoir of DHA, a fatty acid essential for brain development and function.
<>This study joins others that suggest inulin may have deleterious effects. The consequences of these alterations on the physiology and the functioning of the brain, as well as the molecular mechanisms that link inulin/gut microbiota and Pl levels in the brain, remain to be elucidated."[399.1]

Xylooligosaccharide (Xylo)

[A] Xylo enhances Bacteroides Fragilis growth.

"<>This study was conducted to determine the tolerance and effects of the prebiotic xylooligosaccharide (XOS) on the composition of human colonic microbiota, pH and short chain fatty acids (SCFA) in order to determine whether significant changes in the microbiota would be achievable without side effects. Healthy adult subjects ($n = 32$) were recruited in a double-blind, randomized, placebo-controlled study. Subjects received 1.4 g XOS, 2.8 g XOS or placebo in daily doses. The study consisted of a 2 week run-in, an 8 week intervention, and a 2 week washout phase. Stool samples were collected at baseline, after 4 and 8 weeks of intervention and 2 weeks after cessation of intervention. Samples were subjected to culture, pyrosequencing of community DNA, pH and SCFA analyses. Tolerance was evaluated by daily symptom charts. XOS was tolerated without significant gastrointestinal side effects. <>Bifidobacterium counts increased in both XOS groups compared to the placebo subjects, the 2.8 g per day group showed significantly greater

increases than the 1.4 g per day group. Total anaerobic counts and Bacteroides fragilis group counts were significantly higher in the 2.8 g per day XOS group. There were no significant differences in the counts of Lactobacillus, Enterobacteriaceae and Clostridium between the three groups. XOS intervention had no significant effect on stool pH, SCFA or lactic acid. Pyrosequencing showed no notable shifts in bacterial diversity. XOS supplementation may be beneficial to gastrointestinal microbiota and 2.8 g per day may be more effective than 1.4 g per day. The low dose required and lack of gastrointestinal side effects makes the use of XOS as a food supplement feasible."[400]

Malitol

The consumption of Malitol appears to promote Bifidobacterium, Lactobacillus, Bacteroides, and Clostridium growth, making a product like Breyers "Carb Smart" Ice Cream an interesting cheat meat dessert.

<>Sweeteners are being sourced to lower the energetic value of confectionery including chocolates. Some, especially non-digestible carbohydrates, may possess other benefits for human health upon their fermentation by the colonic microbiota. The present study assessed non-digestible carbohydrate sweeteners, selected for use in low-energy chocolates, for their ability to beneficially modulate faecal bacterial profiles in human volunteers.
<>Forty volunteers consumed a test chocolate (low-energy or experimental chocolate) containing 22·8 g of maltitol (MTL), MTL and polydextrose (PDX), or MTL and resistant starch for fourteen consecutive days. The dose of the test chocolates was doubled every 2 weeks over a 6-week period. Numbers of faecal bifidobacteria significantly increased with all the three test treatments. Chocolate containing the PDX blend also significantly increased faecal lactobacilli ($P = 0{\cdot}00\ 001$) after the 6 weeks. The PDX blend also showed significant increases in faecal propionate and butyrate ($P = 0{\cdot}002$ and $0{\cdot}006$, respectively).
<>All the test chocolates were well tolerated with no significant change in bowel habit or intestinal symptoms even at a daily dose of 45·6 g of non-digestible carbohydrate sweetener. This is of importance not only for giving manufacturers a sugar replacement that can reduce energetic content, but also for providing a well-tolerated means of delivering high levels of non-digestible carbohydrates into the colon, bringing about improvements in the biomarkers of gut health."[400.1]

[B] Bacteroides Fragilis is a "**Microbiome-Derived Neurotoxin**". See the correlation with Psyllium Husk.

"<>The microbiome of the human gastrointestinal (GI)-tract is a rich and dynamic source of microorganisms that together possess a staggering complexity and diversity. Collectively these microbes are capable of secreting what are amongst the most neurotoxic and pro-inflammatory biopolymers known. These include lipopolysaccharide (LPS), enterotoxins, microbial-derived amyloids and small non-coding RNA (sncRNA).

One of the major microbial species in the human GI-tract microbiome, about ~100-fold more abundant than Escherichia coli, is Bacteroides fragilis, an anaerobic, rod-shaped Gram-negative bacterium that secretes: (i) a particularly potent, pro-inflammatory LPS glycolipid subtype (BF-LPS); and (ii) a hydrolytic, extracellular zinc metalloproteinase known as B. fragilis toxin (BFT) or fragilysin.
<>Ongoing studies support multiple observations that BF-LPS and BFT (fragilysin) disrupt paracellular barriers by cleavage of intercellular proteins, such as E-cadherin, between epithelial cells, resulting in 'leaky' barriers. These defective barriers, which also become more penetrable with age, in turn permit entry of microbiome-derived neurotoxic biopolymers into the systemic circulation from which they can next transit the blood-brain barrier (BBB) and gain access into the brain. This short communication will highlight some recent advances in this extraordinary research area that links the pro-inflammatory exudates of the GI-tract microbiome with innate-immune disturbances and inflammatory signaling within the human central nervous system (CNS) with reference to Alzheimer's disease (AD) wherever possible."[401]

!!CAUTION!! Psyllium Husk !!CAUTION!!

This fiber is a microbiome toxin abused especially among the elderly.

[A] Psyllium Husk promotes the growth of Bacteroides. OTU = Group of organisms.

"<>The Simpson evenness indices reflected the same observation whereby the microbial evenness was significantly lower in samples with Psyllium husk."
"<>The relative abundance of the OTUs in the genera Bacteroides was significantly higher in samples with Psyllium husk."[402]

[A2] Bacteroides are highly toxic and are associated with pathological aging.

"<>The gut microbiome has important effects on human health, yet its importance in human ageing remains unclear. In the present study, we demonstrate that, starting in mid-to-late adulthood, gut microbiomes become increasingly unique to individuals with age. We leverage three independent cohorts comprising over 9,000 individuals and find that compositional uniqueness is strongly associated with microbially produced amino acid derivatives circulating in the bloodstream. In older age (over ~80 years), healthy individuals show continued microbial drift towards a unique compositional state, whereas this drift is absent in less healthy individuals. The identified microbiome pattern of healthy ageing is characterized by a depletion of core genera found across most humans, primarily Bacteroides. Retaining a high Bacteroides dominance into older age, or having a low gut microbiome uniqueness measure, predicts decreased survival in a 4-year follow-up.
<>Our analysis identifies increasing compositional uniqueness of the gut microbiome as a component of healthy ageing, which is characterized by distinct microbial metabolic outputs in the blood."[403]

Spirulina Platensis

Note: I am including Spirulina Platensis into this section as it is a cyanobacteria, and most likely immunomodulatory by way of the Peyer's patches.

Spirulina appears to reduce the deleterious effects overtraining has on the immune system through suppressing post-exercise increases in Treg counts (Regulatory T-Cells: Anti-Inflammatory: M2 Phenotype). Caution should be used with Spirulina as it may promote autoimmunity.

"<>The results of this study imply that supplementation with SPR extract might prevent a post-exercise increase in Treg counts and a post-recovery decrease in the number of Tδγ cells, which contributed to lower Treg/CTL pre-exercise and post-exercise values ratio during the 2nd examination.
<>Altogether, these findings suggest that supplementation with SPR extract may protect athletes against a deficit in immune function (especially, anti-infectious function) associated with strenuous exercise, and may cause a beneficial shift in an "overtraining threshold" that prevents a radical deterioration of immunity."[405]

[B] Spirulina is a potent immunostimulant.

"<>Participants took a Spirulina supplementation for 12 weeks and were administered

comprehensive dietary questionnaires to determine their nutritional regimen during the study. Complete cell count (CCC) and indoleamine 2,3-dioxygenase (IDO) enzyme activity, as a sign of immune function, were determined at baseline and weeks 6 and 12 of supplementation. Thirty study participants completed the entire study and the data obtained were analyzed. Over the 12-week study period, there was a steady increase in average values of mean corpuscular hemoglobin in subjects of both sexes.
<>In addition, mean corpuscular volume and mean corpuscular hemoglobin concentration also increased in male participants. Older women appeared to benefit more rapidly from Spirulina supplements. Similarly, the majority of subjects manifested increased IDO activity and white blood cell count at 6 and 12 weeks of Spirulina supplementation. Spirulina may ameliorate anemia and immunosenescence in older subjects. We encourage large human studies to determine whether this safe supplement could prove beneficial in randomized clinical trials."[406]

[C] Spirulina stimulates anabolism moreso than casein.

"<>Young (30 days) Wistar rats were fed, during 60 days, with 17% protein spirulina (S) and compared to rats fed 17% protein casein (C). We evaluated the muscle total protein and DNA contents and the in vitro protein synthesis and degradation rates as well the myosin protein expression. The groups presented similar body weight (C = 427.3 +/- 8.6; S = 434.6 +/- 7.7 g) and length (C = 25.4 +/- 0.2; S = 25.6 +/- 0.2 cm). Soleus muscle

total protein (C = 2.9 +/- 0.1; S = 2.7 +/- 0.1 mg/100 mg) and DNA (C = 0.084 +/- 0.005; S = 0.074 +/- 0.005 mg/100 mg) contents were also similar in both groups. Protein degradation (C = 427.5 +/- 40.6; S = 476.7 +/- 50.5 pmol/mg(-1) h(-1)) did not differ between the groups but protein synthesis (C = 17.5 +/- 1.0; S = 25.2 +/- 1.9 pmol/mg(-1) h(-1)) and myosin content (western blot analyses) were higher ($P < 0.05$, t test) in spirulina group.
<>Conclusions: Although the spirulina proved adequate protein quality to maintain body growth, the muscle protein synthesis rates were increased by the ingestion of the experimental diet in young rats."[407]

Lactose

Lactose is a wonderful prebiotic that our ancestors have consumed for thousands of years[A]. Although dairy is a large source of Palmitic acid, the benefits appear to outweigh the negatives, and considering that low fat or fat free dairy products are now commonly available in grocery stores, there is no excuse not to consume dairy products, most especially fat free milk, low fat kefir, low fat cottage cheese, and fat free yogurt. I would never suggest consuming large amounts of Lactose with expensive supplements or prescription drugs, but at the very least while not on a carb-restricted diet we should have one day a week wherein we consume this excellent prebiotic sugar.

It must be mentioned that to deprive yourself, or a child of Dairy (Lactose) in favor of high oleic acid or estrogenic plant milks (not including Coconut milk, or Ripple Milk) will perturb their developing immunological-neurological health by reducing the abundance of beneficial bacteria in their intestines, thus increasing their risk for developing behavioral issues in later life due to an increased tendency to develop subtle or chronic dysbiosis.

[A] "<>Introduction: Following consumption of milk, lactose, a disaccharide of glucose and galactose, is hydrolyzed and absorbed in the upper gastrointestinal tract. However, hydrolysis and absorption are not always absolute, and some lactose will enter the colon where the gut microbiota is able to hydrolyze lactose and produce metabolic byproducts.
<>Methods: Here, the impact of lactose on the gut microbiota of healthy adults was examined, using a short-term, in vitro strategy where fecal samples harvested from 18 donors were cultured anaerobically with and without lactose. The data were compiled to identify donor-independent responses to lactose treatment.
<>Results and discussion: Metagenomic sequencing found that the addition of lactose decreased richness and evenness, while enhancing prevalence of the β-galactosidase gene. Taxonomically, lactose treatment decreased relative abundance of Bacteroidaceae and increased lactic acid bacteria, Lactobacillaceae, Enterococcaceae, and Streptococcaceae, and the probiotic Bifidobacterium. This corresponded with an increased abundance of the lactate utilizers, Veillonellaceae. These structural changes coincided with increased total short-chain fatty acids (SCFAs), specifically acetate, and lactate.

<>These results demonstrated that lactose could mediate the gut microbiota of healthy adults in a donor-independent manner, consistent with other described prebiotics, and provided insight into how dietary milk consumption may promote human health through modifications of the gut microbiome."[410.1]

[B] Unexpectedly, Milk Proteins are digested in self-reported lactose-intolerant individuals. This does not mean lactose intolerance will not affect prescription or supplement absorption, but it's interesting research.

"<>Background/objectives: Self-reported digestive intolerance to dairy foods is common. As dairy can be an important source of dietary protein, this study aimed to identify whether milk protein digestion is compromised in individuals with digestive intolerance. <>Subjects/methods: Adult women (n = 40) were enroled in this double-blinded, randomised cross-over trial, with digestive symptoms characterised using a lactose challenge and self-reported digestive symptom questionnaire. Participants were classified as either lactose intolerant (LI, n = 10), non-lactose dairy intolerant (NLDI, n = 20) or dairy tolerant (DT, n = 10). In a randomised sequence, participants consumed three different kinds of milk (750 ml); conventional milk (CON), a2 Milk™ (A2M), and lactose-free conventional milk (LF-CON). Circulatory plasma amino acid (AA) concentrations were measured at baseline and every 30 min until 3 h post-ingestion. Results: In all participants across all milk types, plasma AA concentrations (AUC0-180) increased after milk ingestion with no significant differences in responses observed between milk types or participants ($P > 0.05$), with the exception of the suppressed lysine response in the DT group following A2M ingestion, relative to the other two groups and milk types ($P < 0.05$).
<>Conclusion: Milk protein digestion, as determined by circulatory AAs, is largely unaffected by dairy- and lactose- intolerances."[410.1A]

[C] Lactose intolerant subjects appear to have an altered microbiome compared to habitual milk consumers, which of course aligns with study [A]. The less lactose you consume, the greater issue you will have digesting it.
Interestingly, this study suggests that it is possible that a diet higher in fiber, and lower in protein, will result in flora changes that result in less efficient protein absorption.

"<>Many healthy people suffer from milk-related gastrointestinal discomfort (GID) despite not being lactose intolerant; the mechanisms underpinning such condition are unknown. This study aimed to explore milk protein digestion and related physiological responses (primary outcome), gut microbiome and gut permeability in 19 lactose-tolerant healthy nonhabitual milk consumers [NHMCs] reporting GID after consuming cow milk compared to 20 habitual milk consumers [HMCs] without GID. NHMCs and HMCs participated in a milk-load (250 mL) test, underwent blood sample collection at 6 time points over 6 h after milk consumption and collected urine samples and GID self-reports over 24 h.

<>We measured the concentrations of 31 milk-derived bioactive peptides (BAPs), 20 amino acids, 4 hormones, 5 endocannabinoid system mediators, glucose and the dipeptidyl peptidase-IV (DPPIV) activity in blood and indoxyl sulfate in urine samples. Subjects also participated in a gut permeability test and delivered feces sample for gut microbiome analysis.
<>Results showed that, compared to HMCs, milk consumption in NHMCs, along with GID, elicited a slower and lower increase in circulating BAPs, lower responses of ghrelin, insulin, and anandamide, a higher glucose response and serum DPPIV activity.
<>The gut permeability of the two groups was similar, while the habitual diet, which was lower in dairy products and higher in the dietary-fibre-to-protein ratio in NHMCs, possibly shaped the gut microbiome; NHMCs exhibited lower abundance of Bifidobacteria, higher abundance of Prevotella and lower abundance of protease-coding genes, which may have reduced protein digestion, as evidenced by lower urinary excretion of indoxyl sulfate
<>In conclusion, the findings showed that a less efficient digestion of milk proteins, supported by a lower proteolytic capability of the gut microbiome, may explain GID in healthy people after milk consumption."[410.1B]

Meat Proteins & Soy Protein

Meat Proteins, although digestible, exert prebiotic effects on the intestinal microbiome. Chicken protein appears to enhance Lactobacillus growth, Beef protein & Casein protein enhance Amino Acid digestion through promoting the growth of certain bacteria, whereas the long-term consumption of Soy Protein reduces Lactobacillus growth, enhances the growth of the Clostridia bacteria Ruminococcus [See: Bonus Information: The Gut Microbiome & Neurodegeneration], while benefiting carbohydrate metabolism, and with long term consumption may cause a systemic *inflammatory* response through promoting CD14 expression, a co-receptor of Toll-like Receptor 4, and this response may enhance fast twitch fiber growth, or early myogenesis, but will lead to sickness in later life (if not mitigated through chronic exercise).

"<>Previous studies have paid much attention to the associations between high intake of meat and host health. Our previous study showed that the intake of meat proteins can maintain a more balanced composition of gut bacteria as compared to soy protein diet. However, the associations between dietary protein source, gut bacteria, and host health were still unclear. In this study, we collected colonic contents from the growing rats fed with casein, beef, chicken or soy proteins for 90 days, and analyzed the compositions of gut microbiota and metabolites.
<>Compared to the casein group (control), the chicken protein group showed the highest relative abundance of Lactobacillus and the highest levels of organic acids, including lactate, which can in turn promote the growth of Lactobacillus. The soy protein group had the highest relative abundance of Ruminococcus but the lowest relative abundance of Lactobacillus. Long-term intake of soy protein led to the up-regulation of transcription factor CD14 receptor and lipopolysaccharide-binding protein (LBP) in liver, an indicator

for elevated bacterial endotoxins. In addition, the intake of soy protein also increased the levels of glutathione S-transferases in liver, which implicates elevated defense and stress responses.
<>These results confirmed that meat protein intake may maintain a more balanced composition of gut bacteria and reduce the antigen load and inflammatory response from gut bacteria to the host.
<>Based on the above results, soy protein intake could induce more carbohydrate metabolism as compared to beef and chicken proteins. Most of the amino acids (AAs) and their related metabolites were more abundant in casein and beef protein groups. The aromatic amino acids, such as phenylalanine and branched-chain amino acids, including valine, leucine, and isoleucine, were also higher in casein protein group. This could be attributed to higher abundance of gut bacteria such as Fusobacterium, which has the capacity of utilizing undigested dietary proteins and producing
amino acids by excreting proteolytic enzymes."[410.2]

Sourdough

Sourdough is a culture of flour and many different Lactobacillaceae strains. Although most of the microorganisms perish in the process of cooking, they appear to exert beneficial effects prematurely to their deaths on the health aspects of bread. The consumption of live culture-made Sourdough bread appears to enhance resistant starch (slow digesting starch), protein breakdown into amino acids, & *may* feed colonic microbiota.

It is a very intriguing idea to attempt to make Sourdough bread with post-cooking live cultures still present, and this may be possible through the use of a large food dehydrator that can operate at temperatures at or below 100 Degrees Fahrenheit (37°C) and a large amount of water and oil added to the dough before cooking. If this is not possible, I hope that new recipes will be invented to incorporate raw sourdough into food.

"<>The contribution of sustainably food processing to healthy intestinal microbial functions is of recent acquisition. The sourdough fermentation fits well with the most sustainable bread making. We manufactured baker's yeast (BYB) and sourdough (t-SB30) breads, which first underwent an in-depth characterization. According to nutritional questionnaires, we selected 40 volunteers adhering to the Mediterranean diet. <>Data on their fecal microbiota and metabolome allowed the selection of two highly representative fecal donors to separately run the Twin Mucosal-SHIME (Twin M-SHIME) under 2-week feeding with BYB and t-SB30. Bread feeding did not affect the microbial composition at phylum and family levels of both donors, in all Twin M-SHIME colon tracts, and lumen and mucosal compartments. The genus core microbiota showed few significant fluctuations, which regarded the relative abundances of Lactobacillus and Leuconostoc according to feeding with BYB and t-SB30, respectively. Compared with BYB, the content of all short chain fatty acids (SCFA), and isovaleric and 2-methylbutyric acids significantly increased with t-SB30 feeding. This was evident for all

Twin M-SHIME colon tracts and both donors. The same was found for the content of Asp, Thr, Glu, GABA, and Orn.
<>The bread characterization made it possible to identify the main features responsible for this metabolic response. Compared with BYB, t-SB30 had much higher contents of resistant starch, peptides, and free amino acids, and an inhomogeneous microstructure. We used the most efficient approach to investigate a staple food component, excluding interferences from other dietary factors and attenuating human physiology overlaps. The daily consumption of sourdough bread may promote the healthy microbiota metabolism at colon level.
<>IMPORTANCE: Knowledge on environmental factors, which may compose the gut microbiota, and drive the host physiology and health is of paramount importance. Human dietary habits and food compositions are pivotal drivers to assemble the human gut microbiota, but, inevitably, unmapped for many diet components, which are poorly investigated individually. Approximately 30% of the human diet consists of fermented foods and beverages. Bread, a fermented/leavened food, is a basic component of the human diet. Its potential effect on gut microbiota composition and functionality is challenging.
<>In this study, we industrially made baker's yeast and sourdough breads, which were used to feed the Twin Mucosal-SHIME, a worldwide scientifically validated gastrointestinal simulator. Only the consumption of sourdough bread has the potential to enhance the synthesis of short chain fatty acids and free amino acids at the colon level."[410.3]

[See: IMC Sciences Overview: Resistant Starch]

Short Chain Fatty Acids

Butyrate

Butyrate appears to be the most beneficial SCFA.

[A] Butyrate enhances lipolysis, likely through the Beta-3 Adrenoreceptor.

"<>What is the central question of this study? Butyrate can prevent diet-induced obesity through increasing energy expenditure. However, it is unclear whether β3 -adrenergic receptors (ARβ3) mediate butyrate-induced adipose lipolysis. What is the main finding and its importance? Short-term oral administration of sodium butyrate is effective in alleviating diet-induced obesity through activation of ARβ3-mediated lipolysis in white adipose tissue. Butyrate can prevent diet-induced obesity through increasing energy expenditure. However, it is unclear whether ARβ3 mediates butyrate-induced adipose lipolysis.
<>In this study, weaned mice were were fed control (Con) or high-fat (HF) diet for 8 weeks to establish obesity. High-fat diet-induced obese mice maintained on the HF diet

were divided into two subgroups; the HFB group was gavaged with 80 mg sodium butyrate (SB) per mouse every other day for 10 days, whereas the HF group received vehicle. Chromatin immunoprecipitation assay was performed to determine the status of histone H3 lysine 9 acetylation (H3K9Ac) on the promoter of the β3 -adrenergic receptor (ARβ3) gene in epididymal white adipose tissue.
<>It was shown that five gavage doses of SB significantly alleviated HF diet-induced obesity and restored plasma leptin concentration to the control level. Protein contents of ARβ3 and PKA, as well as ATGL and p-HSL (Ser563), were significantly upregulated in the HFB group compared with the HF group. Mitochondrial oxidative phosphorylation was enhanced by SB treatment. Sodium butyrate significantly increased the expression of four out of 13 mitochondrial DNA-encoded genes and significantly upregulated the protein contents of peroxisome proliferator-activated receptor-γ coactivator 1α and COX4.
<>Moreover, SB administration enhanced the expression of ARβ3 and its downstream signalling. The G protein-coupled receptor 43 and p-CREB (Ser133) were significantly stimulated by SB. In addition, an active transcription marker, H3K9Ac, was significantly enriched on the promoter of the ARβ3 gene. Our results indicate that short-term oral administration of SB is effective in alleviating diet-induced obesity through activation of the ARβ3-mediated lipolysis in the epididymal white adipose tissue."[411]

[B] Butyrate enhances bDNF/CREB.

"<>In the healthy adult brain, neurogenesis normally occurs in the subventricular zone (SVZ) and hippocampal dentate gyrus (DG). Cerebral ischemia enhances neurogenesis in neurogenic and non-neurogenic regions of the ischemic brain of adult rodents. This study demonstrated that post-insult treatment with a histone deacetylase inhibitor, sodium butyrate (SB), stimulated the incorporation of bromo-2'-deoxyuridine (BrdU) in the SVZ, DG, striatum, and frontal cortex in the ischemic brain of rats subjected to permanent cerebral ischemia. SB treatment also increased the number of cells expressing polysialic acid-neural cell adhesion molecule, nestin, glial fibrillary acidic protein, phospho-cAMP response element-binding protein (CREB), and brain-derived neurotrophic factor (BDNF) in various brain regions after cerebral ischemia.
<>Furthermore, extensive co-localization of BrdU and polysialic acid-neural cell adhesion molecule was observed in multiple regions after ischemia, and SB treatment up-regulated protein levels of BDNF, phospho-CREB, and glial fibrillary acidic protein. Intraventricular injection of K252a, a tyrosine kinase B receptor antagonist, markedly reduced SB-induced cell proliferation detected by BrdU and Ki67 in the ipsilateral SVZ, DG, and other brain regions, blocked SB-induced nestin expression and CREB activation, and attenuated the long-lasting behavioral benefits of SB. Together, these results suggest that histone deacetylase inhibitor-induced cell proliferation, migration and differentiation require BDNF-tyrosine kinase B signaling and may contribute to long-term beneficial effects of SB after ischemic injury."[412]

Acetate

[A] Acetate promotes lipolysis through AMPK expression. Because of this knowledge, it can be said that the dietary consumption of Vinegar is antiaging, and should be an essential dietary component of the elderly, or the obese.

"<>Background/Aims: Acetic acid (AcOH), a short-chain fatty acid, is reported to have some beneficial effects on metabolism. Therefore, the aim of this study was to investigate the regulatory mechanism of acetic acid on hepatic lipid metabolism in BRL-3A cells.
<>Methods: We cultured and treated BRL-3A cells with different concentrations of sodium acetate (neutralized acetic acid) and BML-275 (an AMPKα inhibitor). The total lipid droplet area was measured by oil red O staining, and the triglyceride content was determined by a triglyceride detection kit. We detected mRNA and protein levels of lipid metabolism-related signalling molecules by RT-PCR and Western blot.
<>Results: Acetic acid treatment increased AMPKα phosphorylation, which subsequently increased the expression and transcriptional activity of peroxisome proliferator-activated receptor α and upregulated the expression of lipid oxidation genes. These changes ultimate led to increasing levels of lipid oxidation in BRL-3A cells. Furthermore, elevated AMPKα phosphorylation reduced the expression and transcriptional activity of the sterol regulatory element-binding protein 1c, which reduced the expression of lipogenic genes, thereby decreasing lipid biosynthesis in BRL-3A cells. Consequently, triglyceride content in acetate-treated BRL-3A cells was significantly decreased.
<>Conclusions: These results indicate that acetic acid activates the AMPKα signalling pathway, leading to increased lipid oxidation and decreased lipid synthesis in BRL-3A cells, thereby reducing liver fat accumulation in vitro."[413]

[B] Acetate promotes lipolysis 2.

"<>Acetic acid (AcOH), a main component of vinegar, recently was found to suppress body fat accumulation in animal studies. Hence we investigated the effects of vinegar intake on the reduction of body fat mass in obese Japanese in a double-blind trial.
<>The subjects were randomly assigned to three groups of similar body weight, body mass index (BMI), and waist circumference. During the 12-week treatment period, the subjects in each group ingested 500 ml daily of a beverage containing either 15 ml of vinegar (750 mg AcOH), 30 ml of vinegar (1,500 mg AcOH), or 0 ml of vinegar (0 mg AcOH, placebo). Body weight, BMI, visceral fat area, waist circumference, and serum triglyceride levels were significantly lower in both vinegar intake groups than in the placebo group.
<>In conclusion, daily intake of vinegar might be useful in the prevention of metabolic syndrome by reducing obesity."[414]

[C] Vinegar (Acetate: Acetic Acid) is a potent and easily accessible fat burner, although it will destroy teeth enamel and damage your intestines with continuous use, you will

want to consider washing your mouth out after consuming it with a gram or two of Sodium Bicarbonate (*Baking Soda*) as an acid neutralizer, and cycle its use every few months to avoid excessive tooth erosion and intestinal inflammation.

There is no point in consuming large amounts of vinegar on a dietary protocol composed of excessive amounts of carbohydrates, as this will only result in a counterintuitive physiological response (mTOR vs AMPK), whereas during periods of carbohydrate restriction, and / or Endurance Training, the chronic high dose consumption (1-3tbsp / meal) of a purified and alcohol-free Acetic Acid product such as Distilled White Vinegar will in theory substantially magnify lipolysis.

"<>Erosive tooth wear was diagnosed in the dentition of a 15-year-old girl with a Moroccan background. After an anamnesis, extensive analysis of possible risk factors and a study of the pattern of erosion, it was concluded that the erosive tooth wear was induced by daily consumption of a glass of apple cider vinegar.
<>Further investigation revealed that in North-African culture, women have used apple cider vinegar to achieve weight loss for generations. Bodybuilders are also known to make use of this method of weight reduction."[415]

Propionic Acid

[A] Propionic Acid reduces inflammation (TNF-a), but promotes adipogenesis, providing more evidence for the complexity of inflammation.

"<>Background: Adipose tissue is a primary site of obesity-induced inflammation, which is emerging as an important contributor to obesity-related diseases such as type 2 diabetes. Dietary fibre consumption appears to be protective. Short-chain fatty acids, e.g. propionic acid, are the principal products of the colonic fermentation of dietary fibre and may have beneficial effects on adipose tissue inflammation.
Results: Treatment of adipose tissue explants with propionic acid results in a significant down-regulation of several inflammatory cytokines and chemokines such as TNF-α and CCL5. In addition, expression of lipoprotein lipase and GLUT4, associated with lipogenesis and glucose uptake, respectively, increased. Similar effects on cytokine and chemokine production by macrophages were observed.
<>Conclusion: We show that propionic acid, normally produced in the colon, may have a direct beneficial effect on visceral adipose tissue, reducing obesity-associated inflammation and increasing lipogenesis and glucose uptake. Effects on adipose tissue as a whole are at least partially explained by effects on macrophages but likely also adipocytes are involved. This suggests that, in vivo, propionic acid and dietary fibres may have potential in preventing obesity-related inflammation and associated diseases."[415.1]

[B] Propionic Acid exerts direct neurotoxicity in the brain, and this result is manifested behaviorally as "antisociality", thus again connecting the microbiome to the mind, and

dysbiosis to mental illness. Those with mental illness much first look to their diets for an answer to their pathology if childhood trauma is not a factor in their life.

"<>Autism spectrum disorder is a group of life-long developmental syndromes, characterized by stereotypic behavior, restricted, communication deficits, cognitive and social impairments. Autism spectrum disorder is heritable state, provided by the mutations of well-conserved genes; however, it has been increasingly accepted that most of such states are the result of complex interaction between individual's genetic profile and the environment that he/she is exposed to. Gut microbiota plays one of the central roles in the etiology of autism. Propionic acid is one of the most abundant short-chain fatty acids, made by enteric bacteria. Propionic acid has many positive functions and acts as the main mediator between nutrition, gut microbiota and brain physiology.
<>However, increased level of propionic acid is associated with various neurological pathologies, including autism. It is proposed that some types of autism might be partially related with alterations in propionic acid metabolism. The amygdala, the main component of social brain, via its large interconnections with fronto-limbic neural system, plays one of the key roles in social communications, emotional memory and emotional processing. Social behavior is a hot topic in autism research. As to anxiety, it is not the main characteristics of ASD, but represents one of the most common its co morbidities. Several theoretical reasons compatible with amygdala dysfunction have been suggested to account for socio-emotional disturbances in autism.
<>In the present study, using adolescent male Wistar rats, the effect of acute administration of low dose of propionic acid on social behavior, anxiety-like behavior and the structure/ultrastructure of central nucleus of amygdale was described. In addition to qualitative analysis, on electron microscopic level the quantitative analysis of some parameters of synapses was performed. Behavior was assessed 2, 24 and 48 hours after treatment.
<>The results revealed that even single and relatively low dose of propionic acid is sufficient to produce fast and relatively long lasting (48 h after treatment) decrease of social motivation, whereas asocial motivation and emotional sphere remain unaffected. Morphological analyses of propionic acid-treated brain revealed the reduced neuron number and the increase of the number of glial cells. Electron microscopically, in some neurons the signs of apoptosis and chromatolysis were detected. Glial alterations were more common. Particularly, the activation of astrocytes and microglia were often observed. Pericapillary glia was the most changed. Neuronal, glial and presynaptic mitochondria showed substantial structural diversities, mainly in terms of size and form. Total number of the area of presynaptic profile was significantly decreased. Some axons were moderately demyelinated.
<>In general, the data indicate that even low dose of propionic acid produces in adolescent rodents immediate changes in social behavior, and structural/ultrastructural alterations in amygdala. Ultrastructural alterations may reflect moderate modifications in functional networks of social brain."[416]

Adipocytes, Adipogenesis, Lipolysis, & Macronutrients

The Two Types of Adipocytes

1. **White Adipocytes (White Fat):** The most abundant type of fat in the body, and to be considered a "secretory organ", this is the type of fat that stores excess energy, and releases chemicals to influence levels of inflammation and glucose homeostasis.
2. **Brown Adipocytes (Brown Fat):** The least abundant type of fat in the body, this is fat tissue serves the purpose of thermogenesis, necessary to regulate body temperature in cold climate animals, and infants. Brown adipocytes contain many mitochondria and express high levels of UCP1, which cause proton leaks in cells, leading to a reduction in ATP production, which leads to increased oxygen consumption i.e. increased cellular respiratory activity, and to increased heat production through intracellular proton friction. Because of this, brown adipocytes have a higher metabolic rate and burn calories, instead of storing them, like white adipocytes.
   "Browing" / "Beiging" of Fat: White Adipocytes are capable of converting to Brown Adipocytes from environmental cold exposure (Hypothermia Therapy), Exercise (AMPK, PGC1a), Hormones (T3, IGF-1), and phytochemicals. Interestingly, VEGF may promote the browning of fat, and is also essential for brown fat function:

"<>Vascular endothelial growth factor (VEGF) is critical for angiogenesis, but also has pleiotropic effects on several nonvascular cells. Our aim was to investigate the role of VEGF in brown adipose tissue (BAT). We show that VEGF expression increases 2.5-fold during differentiation of cultured murine brown adipocytes and that VEGF receptor-2 is phosphorylated, indicating VEGF signaling.
<>VEGF increased proliferation in brown preadipocytes in vitro by 70%, and blockade of VEGF signaling using anti-VEGFR2 antibody DC101 increased brown adipocyte apoptosis, as determined by cell number and activation of caspase 3. Systemic VEGF neutralization in mice, accomplished by adenoviral expression of soluble Flt1, resulted in 7-fold increase in brown adipocyte apoptosis, mitochondrial degeneration, and increased mitophagy compared to control mice expressing a null adenovirus. Absence of the heparan sulfate-binding VEGF isoforms, VEGF164 and VEGF188, resulted in abnormal BAT development in mice at E15.5, with fewer brown adipocytes and lower mitochondrial protein compared to wild-type littermates. <>These results suggest a role for VEGF in brown adipocytes and preadipocytes to promote survival, proliferation, and normal mitochondria and development."[416.A]

Adipogenesis

- Adipose Tissue is composed of adipocytes, or fat cells.
- An adipocyte is a cell that contains multiple triglycerides.

- Triglycerides are molecules composed of one glycerol molecule and three fatty acid molecules joined together.
- Triglycerides are formed predominately through the dietary intake of carbohydrates, fatty acids, and triglycerides.
- Excess glucose in the body is converted into fatty acids in the liver in a process called De Novo Lipogenesis. These fatty acids are then bound to glycerol to form triglycerides and stored in adipocytes.
- Excess fatty acids in the body are converted into triglycerides.
- Glycerol is generally absorbed and utilized through the dietary intake of triglyceride-rich foods, such as animal meats, although the body can produce glycerol from glucose, this is called glyceroneogenesis.
- Adipogenesis (fat growth) requires TGF-b, Insulin, or Glucocorticoids (Cortisol) to commence
- Mature adipocytes secrete a myriad of chemicals, many of which are inflammatory, and myogenic, such as: IL-6, IL-1B, & TNF-a.
  [For a full list see Glossary].

Insulin-stimulated Adipogenesis / Adipocyte Hypertrophy:

- **Adipogenesis** = Fat cell differentiation, similar to myogenic hyperplasia.
- **Adipocyte Hypertrophy** = Fat cell growth through the storage of triglycerides, similar to myogenic hypertrophy.

- Insulin stimulates adipogenesis by activating the Akt pathway which increases the expression of the transcription factor CCAAT/enhancer-binding protein beta, which promotes the expression of PPARy.
- C/EBPβ (CCAAT/enhancer-binding protein beta) and C/EBPδ (CCAAT/enhancer-binding protein delta) expression increase early in adipocytes to coordinate the process of adipogenesis, these proteins are similar to the MRF's.
- PPARy promotes adipogenesis through enhancing the efficiency of the transformation of preadipocytes to adipocytes.
- PPARy promotes De Novo Lipogenesis, causing lipid accumulation.
- PPARy promotes Insulin sensitivity by enhancing GLUT4 expression, a glucose lowering transporter contained within cells that is translocated (moved), thereby becoming active and promoting enhanced glucose uptake in adipocytes (and likely skeletal muscle cells, although research is limited).
- Enhanced glucose uptake in adipocytes promotes fatty acid synthesis, glycerol synthesis, and eventually triglyceride synthesis and storage (adipocyte hypertrophy).

Losing fat is a strategy to reduce inflammation & look superficially better but remember that adipose tissue is a secretory organ that releases myogenic chemicals such as

cytokines, therefore if you are obsessed with growing muscle mass, you will do yourself a disfavor by remaining extremely lean.

Forward: Biochemical Macronutrient Metabolism

- Digested Glucose is converted into Pyruvate; this is referred to as Glycolysis. Pyruvate is then further broken down into either Acetyl-CoA or *Lactate.
- Digested Protein, after being denatured (broken down) by Pepsin and Gastric Acid into peptides, are converted to amino acids, many of which are used for Protein Synthesis, and some are converted into Acetyl-CoA.
- Digested Fatty Acids are directly converted to Acetyl-CoA.

1 Glucose molecule > Somatic Cell Mitochondria > 30-32 ATP molecules.

1 Fructose molecule> Liver Mitochondria > 32 ATP molecules + 0.25 Palmitic Acid molecule. (**Yes, Fructose metabolism results in Palmitic acid production**)

1 Palmitic acid molecule > Somatic Cell Mitochondria > 106 ATP molecules.

1 Oleic acid molecule > Somatic Cell Mitochondria > 116 ATP molecules.

1 Linoleic acid molecule > Somatic Cell Mitochondria > 117 ATP molecules.

*Even though glucose can be converted directly to Lactate during Anaerobic (Low Oxygen: High Intensity Exercise) conditions, and this may seem to argue in favor of a high carbohydrate diet or the use of intra-workout glucose drinks, rapid Glycogen exhaustion and exercise-induced hypoglycemia will always result in greater lactic acid formation in muscle during shorter term exercise (under sixty minutes).

The Two Separate Fat Burning Processes

Lipolysis simplified = The Breakdown of Triglycerides to release fatty acids *and* glycerol to increase cellular energy production.

1. **Exercise-induced Lipolysis**: This is a fat burning initiation process that occurs either through Adrenaline and Norepinephrine release, which are *Flight or Fight response* hormones that prepare and facilitate physical performance (survivalism) through activating the Sympathetic Nervous System. Both of these hormones bind to beta-adrenergic receptors on adipocytes, thereby activating the production of an enzyme called Hormone-sensitive lipase (HSL), which once active catalyzes (accelerates) the hydrolysis (breakdown of a chemical bond through interaction with H2O) of triglycerides stored in adipocytes to form fatty acids and glycerol. The liberated free fatty acids are then oxidized by mitochondria, whereas the glycerol produced from lipolysis is transported to the liver to be converted to glucose through a process called

gluconeogenesis, afterwards the glucose is converted into pyruvate, with produces a small amount of ATP, finally the pyruvate is converted into Acetyl-CoA to be utilized by the mitochondria in producing ATP through Beta-oxidation. Increased AMPK expression also plays a role in Exercise-induced Lipolysis, where it increases the uptake of fatty acids into the mitochondria, and therefore increases the possibility of overloading the Citric Acid Cycle, thereby promoting ketone production, AMPK also activates HSL.

2. **Diet-induced Lipolysis**: This fat burning initiation process occurs through increased Glucagon activity and reduced Insulin signaling. Glucagon is released by the pancreas during times of energy deprivation (starvation), where it increases HSL activity to promote the breakdown of fatty acids. When dietary carbohydrates are restricted and blood glucose levels are reduced, Insulin levels decrease, this leads to increased lipolysis by way of a reduction in the disinhibiting lipolytic properties of Insulin. Also, when Insulin levels are decreased in the body Growth Hormone production rises leading to increased HSL activity. Finally, catecholamines increase during periods of hypoglycemia, this is referred to as the *Counter-regulatory Hormone Response* (continue reading).

A clarification of Exercise-intensity and Lipolysis: It is commonly stated that lower intensity forms of aerobic or cardiovascular exercise burn more fat than higher intensity forms of exercise, including high intensity cardio, and strength training, but it is an oversimplification to suggest this. High volume exercise burns more fat on average because of the mitochondrial biogenesis that accompanies it, and because if combined with macronutrient deprivation, especially carbohydrate deprivation, the Counter-regulatory Hormone Response is liable to become active for a longer period of time. High load resistance training does not often burn a sufficient amount of fat because it does not result in mitochondrial biogenesis, it does exhaust both muscle and liver glycogen stores, and due to far less inherent volume (energy requirement) than high volume exercise, such as Endurance Training. High intensity and high load forms of exercise also cause significant amounts of proteolysis, thus leading to elevated blood glucose levels, and the suppression of lipolysis.

A clarification of Mitochondria and Metabolism: Mitochondrial biogenesis does not directly promote lipolysis, it promotes lipolytic efficiency (fatty acid oxidation capability), and cellular health. However, mitochondrial biogenesis does promote lipolysis indirectly, as exercise—and some might argue cognitive—endurance are dependent on mitochondrial function. If mitochondria are damaged or dysfunctional, or there are too few within a cell, they will not be able to effectively metabolize energy, leading to hyperlipidemia, and they will not be able to produce adequate amounts of energy, especially through ketogenesis, leading to diet-induced failure. This is similar to fast twitch fiber glycogen storage capabilities, such that if a person has too few fast

twitch fibers, and consumes an excess amount of carbohydrates post-exercise, they will be more liable to develop hyperglycemia.

The Metabolic Machinery of Lipolysis and Macronutrient Breakdown

1. **Beta-oxidation**: This is the prime late-stage fat burning process that describes the metabolism of fatty acids in our mitochondria, it does not describe the breakdown of triglycerides (fat cells). Beta-oxidation involves fatty acid chains being broken down within mitochondria into Acetyl coenzyme A (Acetyl-CoA) molecules, once liberated most Acetyl-CoA molecules then enter into the Citric Acid Cycle to form the Energy molecules NADH, FADH2, & ATP. NADH / FADH2 are similar to Electron-storing batteries, and they must be further processed to create ATP. The NADH / FADH2 molecules are sent into the Electron Transport Chain (ETC) where they generate an Electric field, which transfers energy to an adjacent Proton Pump, the Proton Pump accumulates Kinetic Energy and utilizes it to form the Proton Gradient, which charges the ATP Synthase machine, where the recycled components of previously used ATP are held (ADP / Pi), which churns out large amounts of ATP as the final stage of energy processing. Electrons are liable to escape (Electron Leakage) during the Electron Transport Chain process, thus leading to the generation of Reactive Oxygen Species, and Protons can also leak during their movement through the Proton Pump, leading to heat generation by way of escaping the ETC and colliding with intracellular molecules.
   Note: Beta-oxidation produces more ATP molecules than glycolysis.
   [See: The Ketogenic Diet: Incomplete Beta-Oxidation]

2. **Ketogenesis:** This is a secondary and potential *result* of the previous process, Beta-oxidation, and is much less common. During Beta-oxidation, Acetyl-CoA can be converted into the "father" ketone body Acetoacetate, which is then converted to the ketones Beta-hydroxybutyrate (BHB) and Acetone. BHB is similar to "*Energy ink*" in my opinion, because it is used to write epigenetic changes on histones (paper) which strengthen gene transcription (genes = a cities construction blueprints, ordinances, regulations). Newly generated BHB molecules diffuse (are shipped) out of the processing plant (mitochondria) and act as a signaling molecule (ink) in the city (cellular nucleus) to activate or silence genes to enhance metabolism and cellular energy efficiency, especially in the brain, where afterwards they return to the factory after their "signaling" ventures and are reformed into Acetyl-CoA molecules. Ketones result in less breakdown products being formed (NADH / FADH2) during metabolism, but they promote greater electron transfer on the Electron Transport Chain by raising NAD+ concentrations in the cell, making their production of ATP greater and more energy efficient i.e. a a more efficient Electron Transport Chain = Less Electron Leakage = Less ROS production, this is referred to as the Ketolytic Pathway. Ketogenesis generally only occurs when blood glucose is low, or when the Citric Acid Cycle is overwhelmed through diet or intense exercise (Rapid lipolysis > excess Acetyl-CoA > Ketosis).

Ketogenesis is dependent on Beta-oxidation's early processing and breakdown of fatty acid chains to Acetyl-CoA but it is distinct process.

Interestingly, **Ketones do not directly burn fat**, some ketones amplify HSL release[1], while others *suppress it*. Ketones are an alternative fuel source for cells that facilitate the lipolytic program directly through HSL release, but also indirectly in the body, by causing decreased reliance on glucose through reduced proteolysis (epigenetic modifications in muscle tissue). When ketones rise in the blood due to either exercise or extended periods of low blood glucose and low insulin levels, and when these ketones active PGC1a, AMPK, or NAD+, this leads to magnified indirect lipolysis.

It is vital to understand that the body will not enter into a state of chronic ketosis until the majority of glycogen stores are depleted, whereas ketone production can be acutely stimulated by way of diet or higher intensity forms of cardiovascular exercise, especially fasted.

[1] "<>Norepinephrine-sensitive lipase activity was measured in rat epididymal fat pads by determining release either of free fatty acids or of glycerol. Stimulation of the lipase activity by norepinephrine in vitro could not be duplicated by injecting norepinephrine into the rats before sacrifice. A reliable method for assay of lipase deactivation rate was developed in which the tissue is incubated for 80 min, norepinephrine is added for a further incubation of 10 min, and the decay of lipase activity is measured during the next 10 min in the absence of hormone. Of the ketone bodies tested, beta-hydroxybutyrate and probably acetoacetate inhibited the activation of lipase by norepinephrine but had no effect on lipase deactivation rate, whereas acetone increased lipase activity stimulated by norepinephrine when tested at the concentration at which acetoacetate gave an inhibition. Substances other than -hydroxybutyrate that produce reduced nucleotides-alpha-glycerophosphate, malate, and ethanol-had no effect on lipase activity as tested in the present system."[416.B]

An Analogy for Beta-Oxidation

A good mechanical analogy is to envision the traditional Beta-oxidation pathway as a conveyer belt within a factory, wherein the fatty acid chains are deposited and conveyed through complex processing and refining machinery. They go from one point of processing to another, until they are converted into wholly different molecules which are eventually used to produce the energy Adenosine Triphosphate (cellular fuel and currency). The pollution (Reactive Oxygen Species) a factory produces is dependent on the amount and type of energy being produced, and is similar to Climate Change on Earth, as humans must learn to adapt to changing weather conditions to survive, so too must mitochondria, and this adaption promotes cellular fitness, depending on the concentration and magnitude of the aforementioned change. If ROS did not exist, mitochondria would never be forced to adapt, therefore our evolution towards what we are today—our supremely impressive mental processing abilities, and motor

coordination—would be delayed, or even terminally arrested. Intermittent spikes of high or chronically low concentrations of stress, of inflammation, are good for an organism.

An Analogy for Ketogenesis

Continuing with the previous line of thought, the Ketogenesis processing machinery is of secondary importance to the "factory" i.e. mitochondria, and is therefore situated below the conveyer belt of traditional Beta-oxidation. If too many Acetyl-CoA molecules are on the primary conveyer belt, when they reach the processing entrance to the Citric Acid Cycle, many of these excess molecules will be pushed or redirected to the lower platform to be processed into ketones. This isn't always a good thing, as demonstrated in diabetic ketoacidosis, or through Substrate Competition. The body prefers to use either lipid or glucose molecules, but not both *in high concentrations* simultaneously, even if the brain functions best on ketones for their high energy efficiency, flooding the body with fatty acids and sugars simultaneously is liable to result in many forms of cellular damage, from AGE formation, to excess ROS production, to Ceramide accumulation. Overeating is thus the most insidious way to damage our bodies and brains and promote a most undesirable form of inflammation.

It's important to understand that if your goal is maximal ketone production, although the body will enter into a pronounced ketogenic state naturally during starvation, or a Zero-K diet, this process is delayed, and to expedite this process one must exercise frequently, with high volume, and consume large amounts of short chain fats such as those found in Coconut oil, ideally MCT oil.

Macronutrients

Macronutrient-induced Cortisol Release

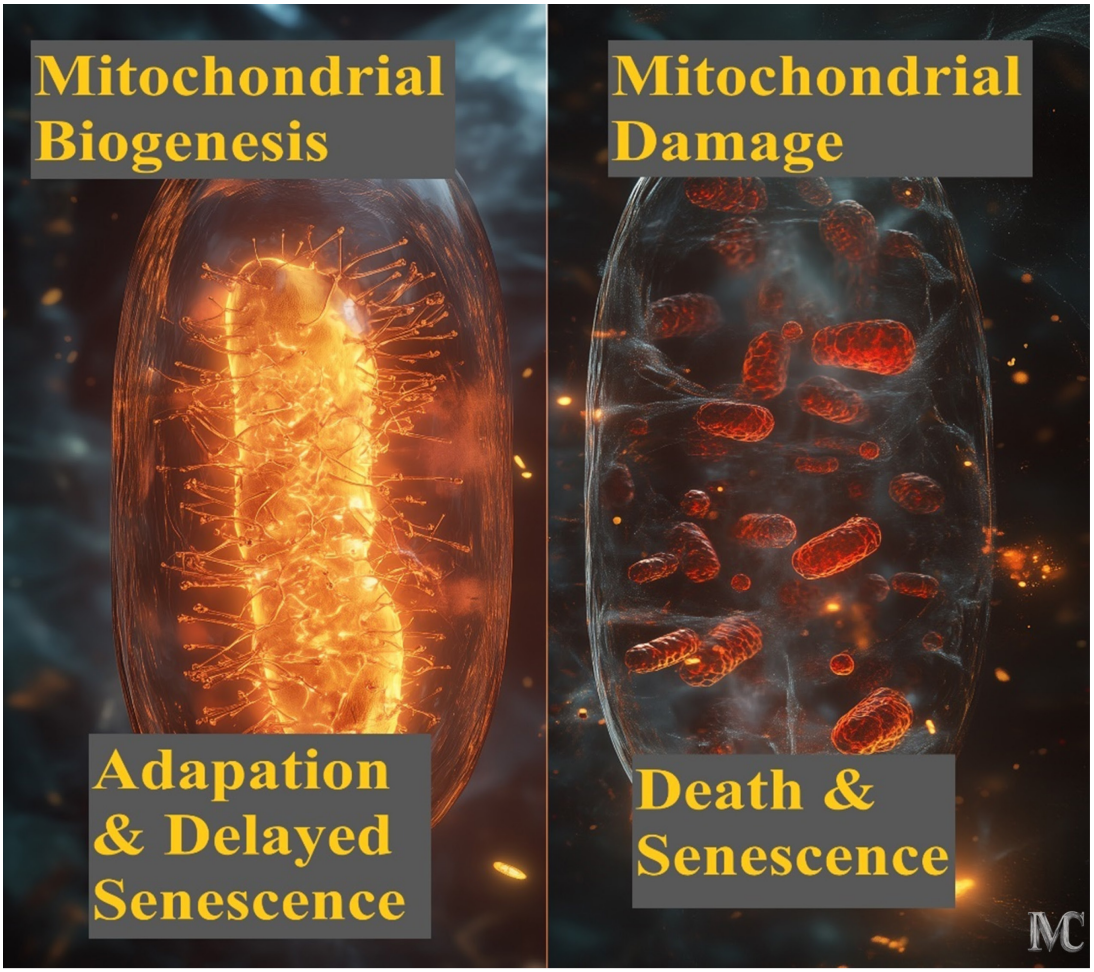
The digestion of macronutrients, primarily protein and carbohydrates, stimulates the release of Cortisol. Smaller and more frequent meals are therefore a healthier option to not only accelerate metabolism but to reduce proteolysis, at the potential cost of reduced anabolic hyperaminoacidemia.

It may seem strange that the body should release a stress hormone after eating, but there are some likely evolutionary explanations; Firstly, Cortisol promotes wakefulness, which would make it a counteractive agent to the fatigueogenic effects of insulin, which promotes serotonin release, and often lulls the mind and body into a false sense of safety. This transient rise in Cortisol would therefore serve the purpose of maintaining neurological arousal levels after eating. Secondly, homeostasis is a phenomenon that describes the bodies attempt to reach balanced biochemical dynamics, and if a rapid influx of immunostimulatory fatty acids enter the body, the body may sense this to be unnatural—or unbalanced, and attempt to suppress immune activity through promoting Cortisol secretion. Luckily, there is no doubt it is possible to suppress to a certain degree this postprandial spike in Cortisol through phytochemical or ergogenic use.

"<>Objective: Hypercortisolism is a risk factor for obesity. Cortisol increases in response to food intake in lean subjects. In obese subjects, disturbances of the food-induced cortisol peak were reported, but data from sufficiently powered and well-controlled trials are lacking. Understanding the cortisol response to food is essential as amplified or recurrent cortisol surges could lead to hypercortisolism and contribute to obesity. Therefore, we investigate the cortisol response to food in lean and obese subjects.
<>Methods: We assessed serum cortisol values after a high-calorie meal in lean and obese male subjects. Cortisol levels were frequently assessed before and for 3 h after food intake.
<>Results: A total of 36 subjects (18 lean and 18 obese) were included. There was no difference in overall cortisol levels between both groups during the study (area under the curve (AUC) obese: 55,409 ± 16,994, lean: 60,334 ± 18,001, P = 0.4). Total cortisol levels reached peak concentrations 20 min after food intake in both groups; the maximum cortisol increase was similar in both groups (cortisol increase obese: 69.6 ± 135.5 nmol/L, lean: 134.7 ± 99.7 nmol/L; P = 0.1). There was no correlation between body mass index and baseline cortisol values (R2 = 0.001, P = 0.83), cortisol increase (R2 = 0.05, P = 0.17), or cortisol AUC (R2 = 0.03, P = 0.28).
<>Conclusions: This study demonstrates that high-calorie food intake causes an immediate and substantial cortisol response in lean and obese subjects and is independent of body weight.
<>Significance statement: This study demonstrates that high-calorie food intake causes an immediate and substantial cortisol response in lean and obese subjects, independent of body weight. In contrast to the current literature, our findings show that the physiological cortisol response to food is intact in obesity. The substantial and prolonged increase further supports the hypothesis that frequent high-calorie meals cause hypercortisolism and aggravate weight gain."[416.C]

Macronutrients & Mitohormesis

Our bodies have adapted to utilize excess carbohydrate-based dietary energy through insulin production, which is beneficial to neurological and myogenic growth, but as we age we should clearly begin to embrace a Low-Carbohydrate / Ketogenic lifestyle as doing so will ensure our cells maintain the necessary levels of autophagy and increased energy efficiency to counteract excessive ROS-induced inflammation and delay the entropic process that propels our cells towards cellular senescence. It may be true that in the majority of cases antioxidant use will delay or suppress Early Hypertrophy due to their inherent anti-inflammatory effects, but as I have mentioned previously it is of absolute necessity to embrace an anti-inflammatory cycle if you suffer from chronic health conditions, as protecting the mitochondria is the ultimate requirement towards *delaying pathological aging*, whereas forming new mitochondria and stronger mitochondria is the ultimate goal of *increasing lifespan*. Cycling between two phases of inflammation appears to me to be the most intelligent way to mitigate the deleterious effects of aging.



These are similar and often overlapping processes, but different in nature and effect, and this is why certain antioxidants have been shown to reduce lifespan in model organisms, as explained in a research study by Colin Selman, Jane S. McLaren, Andrew R. Collins, Garry G. Duthie and John R. Speakman:

"<>While oxidative damage owing to reactive oxygen species (ROS) often increases with advancing age and is associated with many age-related diseases, its causative role in ageing is controversial. In particular, studies that have attempted to modulate ROS-induced damage, either upwards or downwards, using antioxidant or genetic approaches, generally do not show a predictable effect on lifespan. Here, we investigated whether dietary supplementation with either vitamin E (α-tocopherol) or vitamin C (ascorbic acid) affected oxidative damage and lifespan in short-tailed field voles, Microtus agrestis. We predicted that antioxidant supplementation would reduce ROS-induced oxidative damage and increase lifespan relative to unsupplemented controls.
<>Antioxidant supplementation for nine months reduced hepatic lipid peroxidation, but DNA oxidative damage to hepatocytes and lymphocytes was unaffected. Surprisingly, antioxidant supplementation significantly shortened lifespan in voles maintained under both cold (7 ± 2°C) and warm (22 ± 2°C) conditions. These data further question the

predictions of free-radical theory of ageing and critically, given our previous research in mice, indicate that similar levels of antioxidants can induce widely different interspecific effects on lifespan."

↓ continued

"<>In contrast with our previous findings on laboratory mice, our data clearly demonstrate that dietary supplementation with either vitamin E or vitamin C dramatically shortened lifespan in voles. This occurred despite the fact that hepatic lipid peroxidation was significantly reduced in all but one (cold, vitamin C-supplemented) treatment group, although lymphocyte and hepatocyte DNA oxidative damage was unaffected by antioxidant supplementation. The reasons for this lifespan effect are currently unclear.

<>Dietary restriction extends lifespan in many animals, and the antioxidant diets may have been more palatable, driving hyperphagia that potentially affect health and survival. While absolute daily food intake at 11 months of age was unaffected by diet, supplemented voles at both temperatures tended to be heavier than the control animals, although this reached significance, relative to controls, only in the cold exposed vitamin E group. Increased body mass is a major risk factor for many pathologies; hence it would be interesting to know how our antioxidant diets impacted on metabolism and overall health. In addition to a negative impact of antioxidants on lifespan, voles fed the antioxidant-supplemented diets in the cold (where metabolic rate is increased) lived approximately 27 per cent longer than those in the warm. This effect could be mediated via elevated uncoupling of metabolic rate in the cold conditions which has been previously implicated as a factor influencing lifespan. Both the negative impact of antioxidant supplementation and positive effect of cold exposure on lifespan cast further doubt on simplistic models relating metabolism, ROS production and ageing.

<>Antioxidants elicit many cellular effects that are unrelated to ROS-quenching per se, and it is undoubtedly naive to think that other pathways and processes are not affected following supplementation. For example, the positive effects of exercise on insulin sensitivity in humans are lost when antioxidants are given, vitamin C can act as a pro-oxidant under certain conditions, and in yeast, at least, vitamin E supplementation (α-tocopherol) has been shown to increase ROS production, increase oxidative damage and decrease lifespan.

<>In addition, antioxidant efficacy in quenching ROS in vitro appears not to be predictive of lifespan in Caenorhabditis elegans. We did not measure ROS directly or determine endogenous antioxidant levels, hence cannot be certain that antioxidant supplementation did not affect other aspects of antioxidant protection, as seen in mice where lifelong vitamin C supplementation reduced various parameters associated with antioxidant protection.

<>However, it should be noted that this dampening of endogenous antioxidant protection in mice did not have any impact on lifespan. What our findings do indicate is that significant variation exists in the effects of antioxidants on oxidative damage and lifespan across species. We suggest that there is a need for further comparative studies in this area, and that caution should be used when advocating that antioxidants might protect against oxidative damage and ageing in humans, based on studies of limited numbers of species."[416.D]

The Metabolism of Coconut oil Fatty Acids & Uncoupling Protein-1

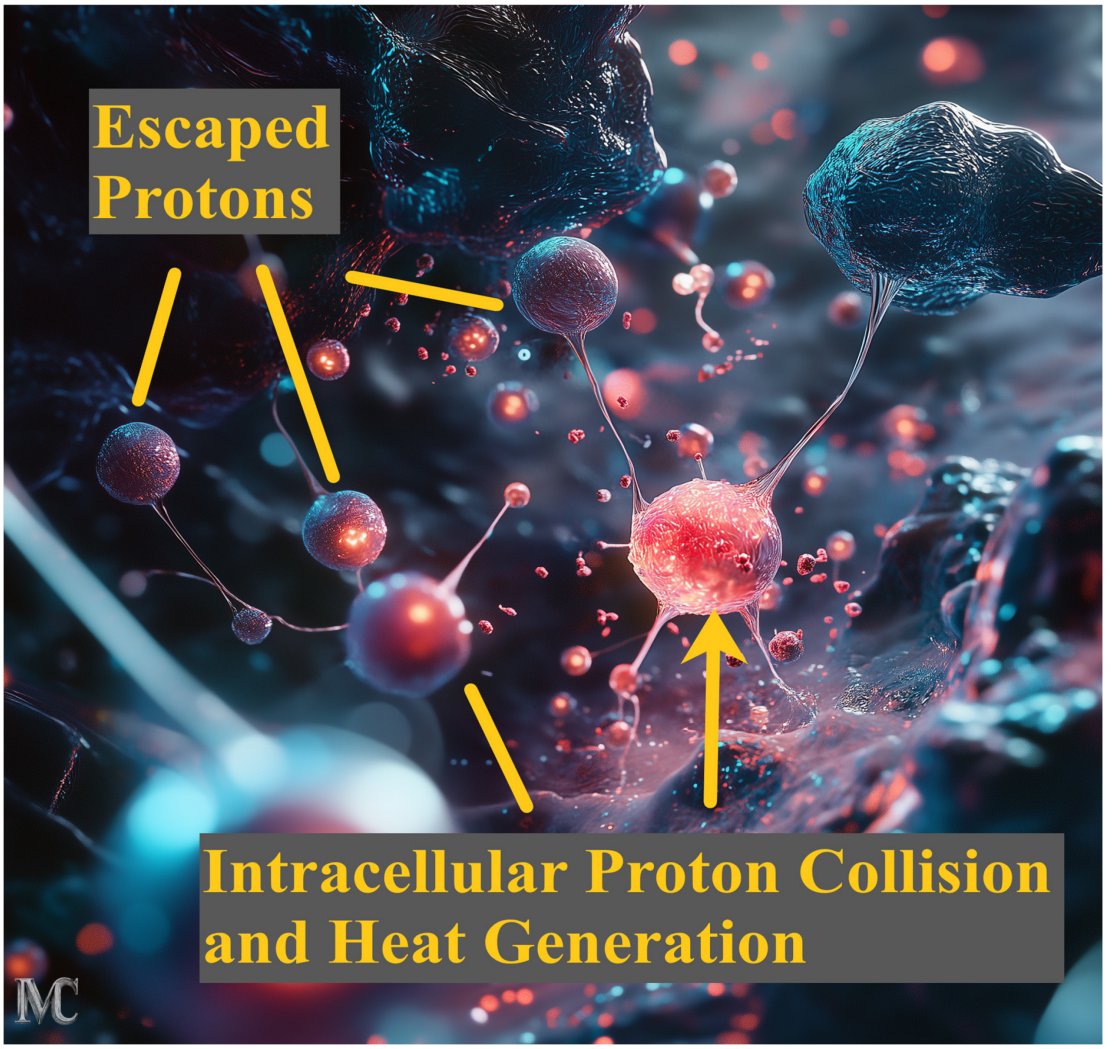
It has puzzled me for quite a while why the consumption of certain fatty acids, such as those found in coconut oil (lauric acid, caprylic acid, capric acid) are said to "burn fat", when they too are broken down into Acetyl-CoA during metabolism, which if in excess can then be converted into triglycerides in the presence or absence of glucose. As it turns out, MCT fatty acids are rapidly metabolized into Acetyl-CoA molecules due to having shorter carbon lengths, thus overloading the Citric Acid Cycle and leading to Ketone production. The ketones then remain in the mitochondria, or return to the mitochondria after their epigenetic duties are completed, and are metabolized in the Ketolytic Pathway. All ketones promote Uncoupling Protein-1 (UCP1) expression, which cause Proton Leakage during their trek through the Ketolytic Electron Transport Chain, which results in less ATP being produced and an energy deficit, leading to increased lipolysis in the presence of a reduced supply of glucose or fatty acids. Proton Leakage is not to be confused with Electron Leakage, Proton Leakage simply reduces ATP yield, whereas Electron Leakage (a byproduct of the primary metabolic fate of carbohydrate and fatty acid breakdown: The Citric Acid Cycle) produces large amounts of ROS because it is less efficient.

The release of escaped Protons results in frictional heat generation within a cell because they rapidly collide with intracellular molecules, such as H2O, proteins, and lipids. Both increased UCP1 expression and intracellular heat generation stimulates the release of transcription factors such as PGC1a which promote mitochondrial biogenesis. This describes a form of Mitohormesis, whereas Electron Leakage-induced ROS heat production although similar, and also capable of promoting mitochondrial biogenesis, is much more capable of damaging mitochondria. Proton Leakage Mitohormesis is thus safer, and more sustainable than Electron Leakage-induced ROS Mitohormesis.

Is it not quite strange that Cellular Respiration, or as I simplify it, *Macronutrient Metabolism*, leads to the production of ROS which may damage the cells from whence they came? There is a reason why those who eat less food often age more gracefully than those who overeat (leaving aside sarcopenia), and it is not simply because of Insulin and mTOR.

You may be wondering, if all fatty acids are broken down into Acetyl-CoA, why would some exert toxic effects in the body, such as Palmitic acid, versus others that exert antioxidant or lipolytic effects in the body such as Alpha-Linoleic acid and MCT's. Well, this can be explained by their *Pre-Metabolic Effects*, where they bind to cell surface receptors, cause epigenetic changes, or cause cell membrane disruption. Also, longer chain fatty acids such as Palmitic acid are preferentially converted into ceramides during metabolism, thus explaining its primary toxicity through the promotion of long lasting and insidious whole body lipid accumulation, which as aforementioned interrupts and dampens cellular signaling, resulting in delayed or suppressed wound healing, and it likely perturbs autophagy too.

It may be possible that someday Coconut fatty acids; Lauric acid, & Caprylic acid / Capric acid i.e. “Medium-chain Triglycerides”, will be considered Essential Fatty acids, considering they promote ketone production, and UCP1 expression, leading to magnified mitochondrial biogenesis, and epigenetic changes, which will invariably delay cellular aging. Of importance, increased UCP1 expression and Proton Leakage will facilitate a slow-twitch phenotype, and this is therefore not ideal for individuals who value muscular explosiveness-power over endurance-strength, but in reality the result of these two processes when activated chronically may simply be the formation or continued facilitation of Hybrid muscle fiber types, depending on training style.



Note: Uncoupling Protein-1 does not only increase due to ketone metabolism, but also through certain phytochemical and ergogenic use, and thermal therapies, such as Silymarin (PTEN), and Hypothermia Therapy. Interestingly, there seems to be a positive physiological trend with Uncoupling Proteins, such as UCP3, which is activated through Glutamine use and is myogenic.

AdipoCycling

I believe it is intelligent to treat adipose tissue as an anabolic factor, one of great complexity and danger, and for those who do not find dieting nor exercise to be difficult, bulking and cutting (myogenesis and lipolysis), are two variables to play with frequently during a lifetime. Cycling between different body fat levels is commonplace among competitive bodybuilders and fitness models, but they rely too heavily on visuality rather than mathematical metrics.

There is in my opinion a "Superficial Limit" (SL) for the fat level of human beings wherein at a certain point of adipogenesis they lose body symmetry, and their traditional superficial beauty begins to fade, paralleling perturbations to both metabolism, and neurological function, but not necessarily myogenesis. Once this hypothetical limit is surpassed the chance of stretch mark formation and skin sagging increases noticeably. I think that this Superficial Limit is at or near 20% Total Body Fat. Once this SL of Body Fat is surpassed comes the magnification of myogenesis and angiogenesis at the cost of superficial beauty and *accelerated aging.

Remember, you can monitor your total fat percentage relatively easily by using a pair of fat calipers and one of the many free online Jackson Pollock three-site or seven-site body fat equation method programs to keep track of your fluctuating fat levels.

It is a grievous mistake to gain *large amounts* of body fat or maintain a high body fat percentage and engage in solely high load resistance training, as many powerlifters and strength athletes do, for they are only taxing their heart, and in this error they shorten their lifespans. Bulking should primarily be performed by those who focus on cardio-based exercise training, where the volume of exercise performed is highly angiogenic, and the ability to accelerate lipolysis is far easier, as they have a greater number of mitochondria, and they can accelerate their metabolisms very easily through training alone. If professional cyclists or runners were to bulk like bodybuilders and powerlifters they would experience large increases in performance during their AdipoCycles, and these benefits would have a carryover effect during *LipoCycles*. Unfortunately, many cardio athletes do not understand the anabolic nature of adipose tissue, and fear gaining weight.

If you prefer traditional strength training, and still wish to experience the benefits of increased fat mass, you should never neglect your steady-state cardio, and the fatter you are, the longer your cardio sessions should be each day to protect your heart and brain from both the increased oxygen demands of adipose tissue and from the unintended consequences of macronutrient excess. [See: ARCS, Cardio, Injuries, & Antagonist Muscle Activation]

It is important to reinstate the fact that adipokines are secreted from adipocytes i.e. fat tissue, not intramuscular lipids. If you consume excess fatty acids, especially Palmitic acid and Oleic acid on a bulking phase, as many athletes and gymgoers often do, you will be perturbing myogenesis and insulin sensitivity in favor of sensory pleasures (better tasting meals). It is therefore important to moderate your intake of non-essential fatty acids, except for of course, Coconut Fatty Acids.

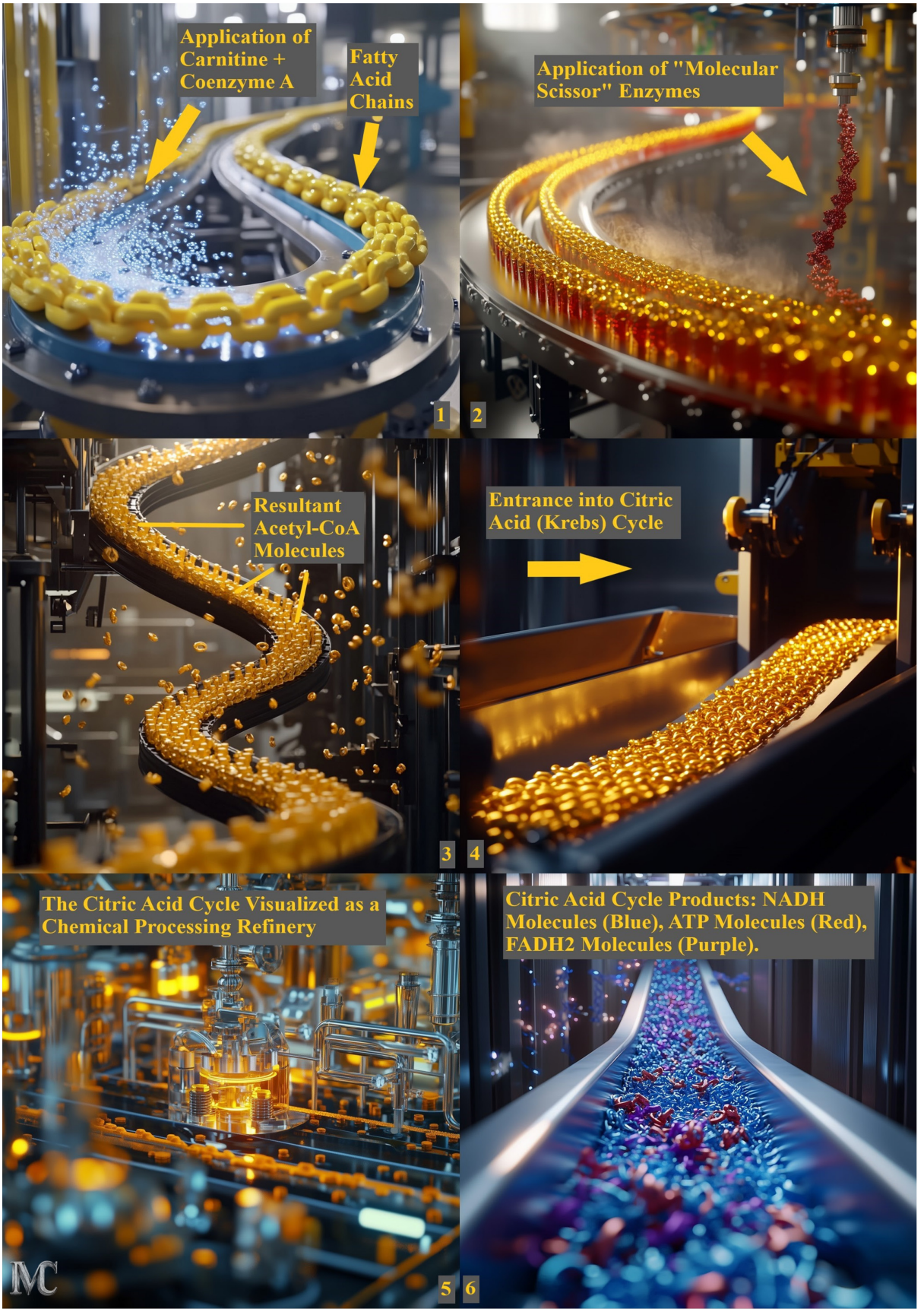
*The acceleration of cellular aging that accompanies higher, but not pathological, total Body Fat percentages is not related to adipokines, as their pro-inflammatory effects can be inhibited through antioxidant use, but moreso in relation to the dietary macronutrient requirements to maintain and grow the aforementioned adipocytes. It is true that the cellular stress of chronically active cellular respiration is one factor in aging, but obesity is also damaging to a body indirectly, as the more food an individual consumes each day will also relate to the total amount of ceramides and AGE's they form and accumulate in their body over time. If an individual "bulks" with healthy macronutrients and monitors their blood sugar they are far less likely to suffer the unintended consequences of purposeful adipogenesis.

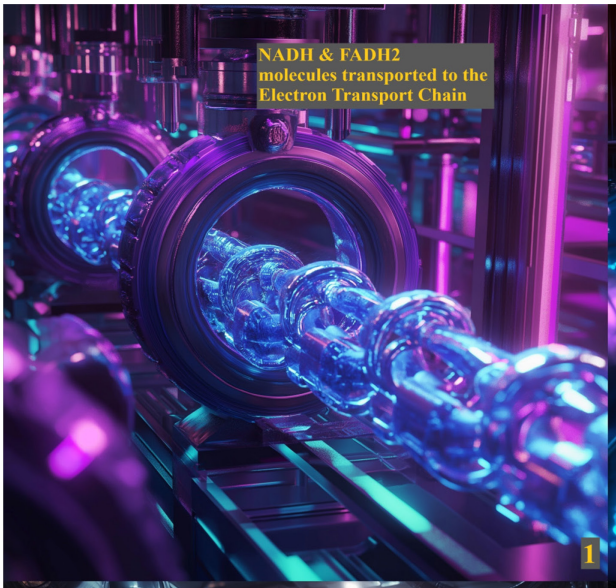
Below are five hypothetical thermodynamic classifications for increasing and decreasing AdipoCycling for the promotion of myogenesis, health, and superficiality:

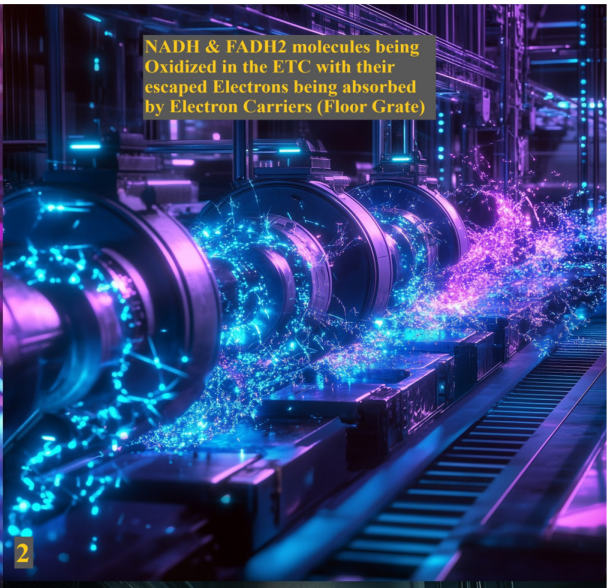
- Hyperendergonic Cycle: 30% Body Fat: Maximally Facilitated Myogenesis.
- Endergonic Cycle: 25% Body Fat: Submaximally Facilitated Myogenesis.
- Isoergic Cycle: 20% Body Fat (**SL**): Strongly Facilitated Myogenesis.
- Exergonic Cycle: 15% Body Fat: Moderately Facilitated Myogenesis.
- Hyporexergonic Cycle: 5-10% Body Fat: Weakly Facilitated Myogenesis.

[See: ARCS, Cardio, Injuries, & Antagonist Muscle Activation: Fat Percentage-based Cardio]

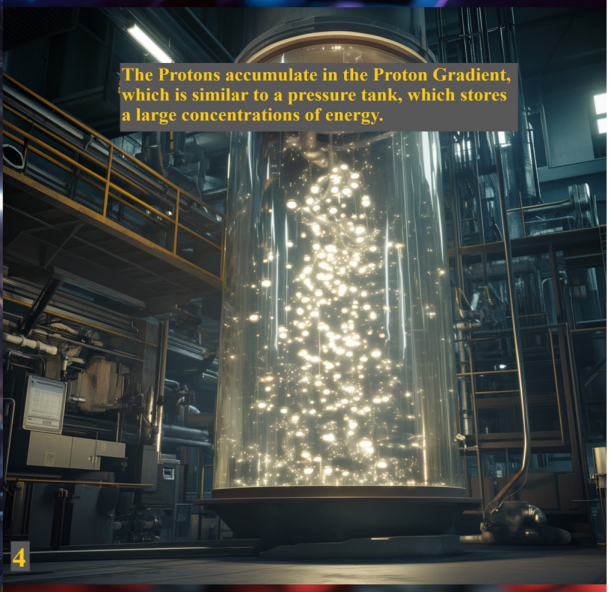
See following pages for my visualizations of Beta-Oxidation, Ketogenesis, & the Ketolytic Pathway.


Application of Carnitine + Coenzyme A
Fatty Acid Chains
1
Application of "Molecular Scissor" Enzymes
2
Resultant Acetyl-CoA Molecules
3
Entrance into Citric Acid (Krebs) Cycle
4
The Citric Acid Cycle Visualized as a Chemical Processing Refinery
5
Citric Acid Cycle Products: NADH Molecules (Blue), ATP Molecules (Red), FADH2 Molecules (Purple).
6


NADH & FADH2
molecules transported to the
Electron Transport Chain
1


NADH & FADH2 molecules being
Oxidized in the ETC with their
escaped Electrons being absorbed
by Electron Carriers (Floor Grate)
2

Electron Carriers (Top Tube)
transfering collected Electrons
adjacent to the Proton Pump,
exchanging Kinetic Energy
with Protons.
3


The Protons accumulate in the Proton Gradient,
which is similar to a pressure tank, which stores
a large concentrations of energy.
4

The Proton Gradient fuels the activity of
ATP Synthase which is similar to a turbine
or generator, and outputs ATP.
5

ATP is an essential energy source for
many biological processes such as protein
synthesis, muscle contraction, and
neurotransmitter release, among others.
6

Entrance of Acetyl-CoA molecules into alternative Ketolytic Pathway
1
Transformation of Acetyl-CoA molecules into Ketones
2
Citric Acid Cycle Pollution (increased ROS generation)
Ketolytic Processing Pollution (reduced ROS generation)
3
Ketone "Energy Ink" processed and prepared to be diffused (shipped out)
4
Ketone Ink entering the Nucleus (City Center) for Epigenetic modification
5
The Ketone Ink being used to write Epigenetic Modifications (City plans, Architecture schematics, Regulation changes)
The Paper = Histones (Epigenetic Writing Area)
6

Adipocyte Cell Death

Adipocytes do not die during lipolysis or beta-oxidation, they only atrophy, just as myotubes atrophy during extended detraining. Only increased levels of inflammatory factors such as Caspase-3, IL-6, TNF-a, and possibly ROS lead to adipocyte death either through initiating apoptosis or necrosis.

Interestingly, it can be hypothesized that in individuals without an adequate number of fat cells, who consume copious amounts of carbs and fats, the excess energy consumed being unable to be stored as fat remains in the bloodstream, eventually causing diabetes, or worsening diet-induced neurological decline, and causing other pathological conditions. On the other hand, individuals who have too many fat cells will find weight loss tremendously difficult, owing to the sheer amount of stored lipids present in their fat tissue.

Four important notes on Lipolysis:

1. There is superb merit to the idea of "bulking" or "adipogenesis" during an intense workout protocol.
2. Lipolysis will be suppressed if insulin (the primary adipogenic hormone) rises significantly after a meal.
3. Interleukin-6 is a very important factor in exercise-induced lipolysis; therefore, it will be of greater difficulty to burn fat on an Anti-Inflammation Cycle as most phytochemicals inhibit it.
4. Because Glycine suppresses AMPK[131.5A], and most other amino acids cause a differential rise in insulin when consumed, it is important to avoid consuming *excess* amounts of amino acids in your diet, and to avoid consuming large amounts of fast digesting proteins such as protein powders. One could eliminate protein powders altogether if they wish to accelerate lipolysis to a greater degree during a lipolytic diet / exercise protocol, but I would never suggest Strength Training without the addition of copious amounts of Pre/Intra/Post-workout protein powder.
5. Restraining mTOR expression through amino acid restriction, after the obligatory restriction or elimination of carbohydrates, and fatty acids (primarily non-essential), when combined with Endurance Training, is a necessary step in maximizing lipolysis, but restricting dietary protein should only be a strategy used by individuals with a moderate-high level of skeletal muscle mass, never in frail individuals. It is better to be overweight and muscular in old age than extremely lean, hunch backed, & sarcopenic, and inevitably end up in an assisted living home, lonely, and likely verbally or physically abused by nursing staff.

The amount of fat burned after a month of dieting and exercise can seem underwhelming, and dissuade people from continuing a lipolysis protocol of specialized dieting and exercise, because we are conditioned to believe through reality TV that we can burn *dozens of pounds* of fat per month, but when a morbidly obese person on a TV show drops five, ten, or fifteen pounds of weight within a relatively short period of time, a

large percentage of that weight loss is fecal matter and water weight (fluid retention). It is more reasonable & healthier to expect to burn between one-four pounds of fat every month on a serious exercise and diet protocol.

Please understand that if losing fat is your ultimate goal, beyond muscle growth, or muscle function (strength, power, etc.), and you engage in very little cardio training because you assume that strength training burns more "calories" than cardio training, you are terribly misinformed. Only high repetition exercise results in efficient skeletal muscle mitochondrial biogenesis and glycogen exhaustion, and with these adaptive processes comes accelerated metabolism, and therefore lipolysis.

Most of us unconsciously prefer classical strength training i.e. performing sets of six, ten, or twelve repetitions, because even if we are forced to strain, it is still *easier* on our minds than cardiovascular training. For cardiovascular training, being nothing more than low load, extremely high-volume resistance training, results in the greatest benefits to the mind—to the promotion of consciousness. Those who do not want to be conscious of their *failures*, and their *weaknesses*, will always avoid all forms of cardio, because when the brain is activated, the equilibrium of thought is shifted towards a more logical, self-critical, and anxiogenic place. If you truly "hate" cardio, even the types of cardio that do not involve large amounts of lactic acid accumulation, you must ask yourself if you instead hate yourself or your life, and if so, why?

As for measuring fat loss, I suggest purchasing a pair of inexpensive fat calipers and using an online and free online Jackson Pollock three-site, or ideally seven-site body fat equation method every week or every month to track your fat loss progress in a journal with progress pictures of yourself in underwear stored digitally.

Cardiovascular exercise is obviously one of the most effective ways to accelerate lipolysis, especially when performed twice a day[1] as the research suggests, when the exercise sessions are split up, and an hour of rest is added between each workout, the result is magnified lipolysis. Whether this magnified exercise-induced lipolytic effect is because of an interaction with insulin, GH, norepinephrine, or IL-6, is unimportant, because the end-result is all that matters.

In study [1], we learn that engaging in two or more cardio sessions per day is an effective way to accelerate lipolysis, although the following study describes the second cardio training session as being performed exactly 60-Minutes (Rest) after the first, the already well-documented adaptive increase in fat oxidation that occurs in the human body post-exercise will not be heavily dampened by training four, six, eight, or ten hours after the first session.

There is a reason why "Golden Era" Bodybuilders were so lean, and it is not only because of the high-volume training, or low carbohydrate diets, but because of their *twice a day* workout splits.

[1] "<>The goal of the study was to examine whether lipid mobilization from adipose tissue undergoes changes during repeated bouts of prolonged aerobic exercise. Microdialysis of the subcutaneous adipose tissue was used for the assessment of lipolysis; glycerol concentration was measured in the dialysate leaving the adipose tissue. Seven

male subjects performed two repeated bouts of 60-min exercise at 50% of their maximal aerobic power, separated by a 60-min recovery period. The exercise-induced increases in extracellular glycerol concentrations in adipose tissue and in plasma glycerol concentrations were significantly higher during the second exercise bout compared with the first ($P < 0.05$). The responses of plasma nonesterified fatty acids and plasma epinephrine were higher during the second exercise bout, whereas the response of norepinephrine was unchanged and that of growth hormone lower. Plasma insulin levels were lower during the second exercise bout. The results suggest that adipose tissue lipolysis during aerobic exercise of moderate intensity is enhanced when an exercise bout is preceded by exercise of the same intensity and duration performed 1 h before. This response pattern is associated with an increase in the exercise-induced rise of epinephrine and with lower plasma insulin values during the repeated exercise bout."[416.E]

Regarding Thyroid Hormone (Triiodothyronine), it is true that it is a lipolytic hormone, but the risk for thyroid cancer or autoimmunity is too high to suggest using it in large dosages for ergogenic purposes such as bodybuilders do.

Although it is extremely vital that if you are having trouble losing weight, even after restricting your carbohydrate and fatty acid consumption and exercising daily, or if you find yourself binge eating carbohydrate-rich meals, even when you are not psychologically stressed, you may have a pathological thyroid condition, for obscure research has shown me that a diet high in carbohydrates enhances Triiodothyronine (T3) production[1], which leads to an increased need of Iodine, thus *the process of overeating may signal thyroid dysfunction*. Therefore, if you are obese it would be wise to have your thyroid examined by ultrasound, not only bloodwork, to check for signs of Hashimoto's disease.

In terms of dosages, I would suggest 1.6-2.0mcg per kg of Levothyroxine (T4) per day. Because T4 is the precursor to T3, and T3 is the chemical responsible for the physiological effects of thyroid hormone, I suggest pushing for higher dosages of over 100mcg of Levothyroxine for the average adult to reach peak levels of mind and body rejuvenation.

[1] "<>An increased iodine requirement as a result of significant changes in human nutrition rather than a decreased environmental iodine supply is suggested to represent the main cause of the iodine deficiency disorders (IDD). The pathomechanism proposed is based on the fact that serum concentrations of thyroid hormones, especially of trijodothyronine (T3), are dependent on the amount of dietary carbohydrate. High-carbohydrate diets are associated with significantly higher serum T3 concentrations, compared with very low-carbohydrate diets. While our Paleolithic ancestors subsisted on a very low carbohydrate/high protein diet, the agricultural revolution about 10,000 years ago brought about a significant increase in dietary carbohydrate. These nutritional changes have increased T3 levels significantly. Higher T3 levels are associated with an enhanced T3 production and an increased iodine requirement. The higher iodine requirement exceeds the availability of iodine from environmental sources in many regions of the world, resulting in the development of IDD."[416.F]

Serine enhances sphingolipid biosynthesis, which are chemicals that bind to fatty acids to form ceramides, but this should not dissuade its use as Serine deficiency causes an even more toxic form of lipid accumulation to occur.

“<>l-Serine is required to synthesize membrane lipids such as phosphatidylserine and sphingolipids. Nevertheless, it remains largely unknown how a diminished capacity to synthesize l-serine affects lipid homeostasis in cells and tissues. Here, we show that deprivation of external l-serine leads to the generation of 1-deoxysphingolipids (doxSLs), including 1-deoxysphinganine, in mouse embryonic fibroblasts (KO-MEFs) lacking d-3-phosphoglycerate dehydrogenase (Phgdh), which catalyzes the first step in the de novo synthesis of l-serine. A novel mass spectrometry-based lipidomic approach demonstrated that 1-deoxydihydroceramide was the most abundant species of doxSLs accumulated in l-serine-deprived KO-MEFs.
<>Among normal sphingolipid species in KO-MEFs, levels of sphinganine, dihydroceramide, ceramide, and hexosylceramide were significantly reduced after deprivation of external l-serine, whereas those of sphingomyelin, sphingosine, and sphingosine 1-phosphate were retained. The synthesis of doxSLs was suppressed by supplementing the culture medium with l-serine but was potentiated by increasing the ratio of l-alanine to l-serine in the medium. Unlike with l-serine, depriving cells of external l-leucine did not promote the occurrence of doxSLs.
<>Consistent with results obtained from KO-MEFs, brain-specific deletion of Phgdh in mice also resulted in accumulation of doxSLs in the brain. Furthermore, l-serine-deprived KO-MEFs exhibited increased formation of cytosolic lipid bodies containing doxSLs and other sphingolipids. These in vitro and in vivo studies indicate that doxSLs are generated in the presence of a high ratio of l-alanine to l-serine in cells and tissues lacking Phgdh, and de novo synthesis of l-serine is necessary to maintain normal sphingolipid homeostasis when the external supply of this amino acid is limited.”[416.G]

REPEATED FOR EFFECT: Insulin suppresses Lipolysis.

"<>This study confirms the presence of glycerol release in skeletal muscle. Lipolysis in skeletal muscle and adipose tissue are suppressed similarly by minute and physiological increases in insulin but differently by supraphysiological increases. Inadequate suppression of intramuscular lipolysis resulting in increased availability of non-esterified fatty acids, could represent a potential mechanism involved in the pathogenesis of impaired glucose disposal, i.e., insulin resistance, in muscle."[417]

Insulin suppresses GH release.
“<>IGF-I is considered a primary inhibitor of GH secretion. Insulin may also play an important role in regulating GH levels because insulin, like IGF-I, can suppress GH synthesis and release in primary pituitary cell cultures and insulin is negatively correlated with GH levels in vivo. However, understanding the relative contribution insulin and IGF-I exert on controlling GH secretion has been hampered by the fact that circulating

insulin and IGF-I are regulated in parallel and insulin (INSR) and IGF-I (IGFIR) receptors are structurally/functionally related and ubiquitously expressed. To evaluate the separate roles of insulin and IGF-I in directly regulating GH secretion, we used the Cre/loxP system to knock down the INSR and IGFIR in primary mouse pituitary cell cultures and found insulin-mediated suppression of GH is independent of the IGFIR. In addition, pharmacological blockade of intracellular signals in both mouse and baboon cultures revealed insulin requires different pathways from IGF-I to exert a maximal inhibitory effect on GH expression/release. In vivo, somatotrope-specific knockout of INSR (SIRKO) or IGFIR (SIGFRKO) increased GH levels.
<>However, comparison of the pattern of GH release, GH expression, somatotrope morphometry, and pituitary explant sensitivity to acute GHRH challenge in lean SIRKO and SIGFRKO mice strongly suggests the primary role of insulin in vivo is to suppress GH release, whereas IGF-I serves to regulate GH synthesis. Finally, SIRKO and/or SIGFRKO could not prevent high-fat, diet-induced suppression of pituitary GH expression, indicating other factors/tissues are involved in the decline of GH observed with weight gain."[417.0]

The Counter-regulatory Hormone Response (CRH)

When hypoglycemia (low blood sugar) occurs the biological *Counter-regulatory Hormone Response* is initiated, which stimulates the release of Counter-regulatory hormones such as Adrenaline, Noradrenaline, Growth Hormone, Cortisol, and Glucagon. This response is necessary for both diet-induced & exercise-induced lipolysis, as these hormones mobilize energy reserves to provide energy to the body during times of severe energy deprivation. All of the aforementioned hormones, stimulate lipolysis through activation of Hormone-Sensitive Lipase.

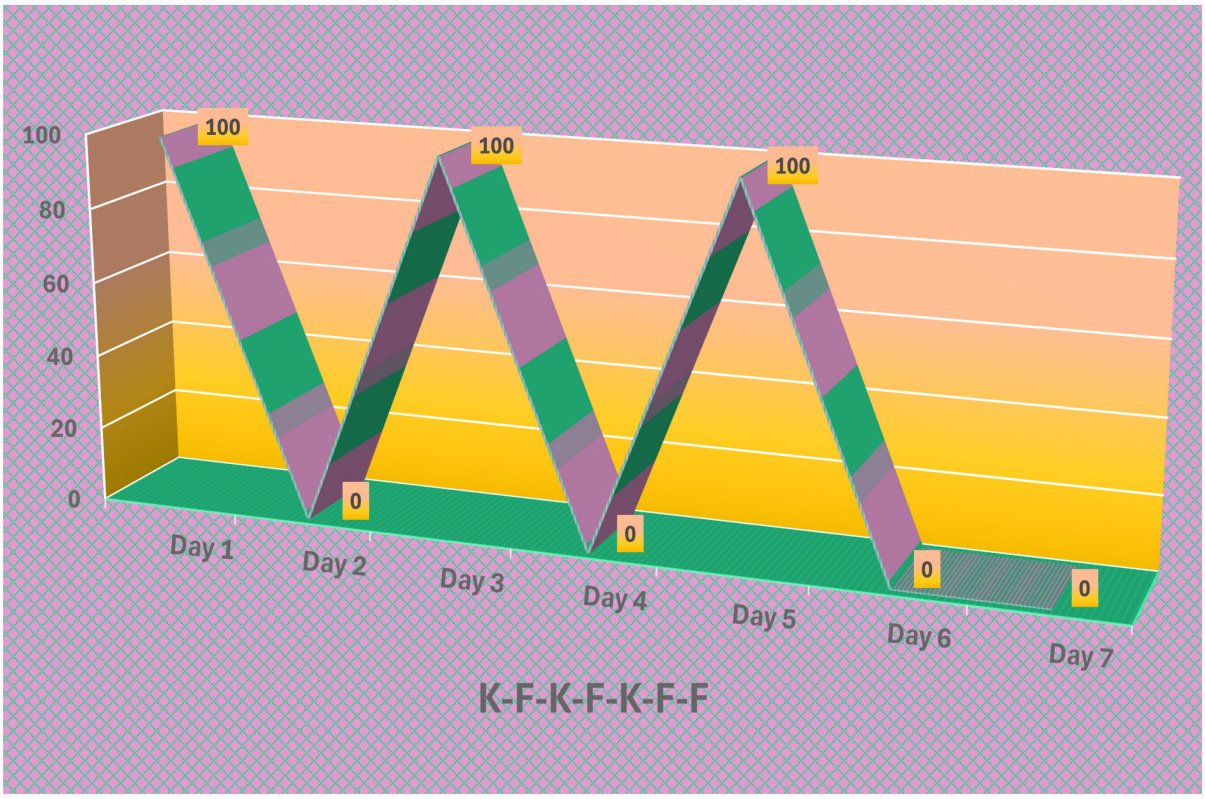
To stimulate the Counter-regulatory Hormone Response without dietary changes requires chronic exercise, although this is quite obvious to me, not many individuals think deeply about the hormonal cascades of exercise and hypoglycemia. If we combine fasting with chronic exercise, we are able to maximize the Counter-regulatory Hormone Response, leading the mobilization and breakdown of far more fat in our bodies than the clichéd and comfortable fasting-while-being-inactive, which is quite counterintuitive to the primary lipolytic point of it all. The idea of fasting while exercising is also strengthened by the fact that the hormones of the CRH Response stimulate *autophagy*, with autophagy being often unconsciously understood but misattributed as the vague term "detoxification" by intuitive but unscientific minds. Blood sugar drops experienced during exercise, if controlled, should not be feared for this reason.

Morning, Afternoon, & Evening Cumulative Oxidation Training © (MAECO)

Every cardiovascular workout results in the promotion of a certain amount of fat oxidation intra-exercise and post-exercise, but there exists a cumulative effect that primes

the body for increased lipolysis with each concurrent cardiovascular exercise session performed within a 12-hour (possibly 24-hour) period [416.0.1]. This is why it is logical to suggest that if three mirrored high volume and intensity cardio sessions are performed in a single day, spread out evenly i.e. Morning, Afternoon, & Evening, fat oxidation will be magnified to a far greater extent as compared to extended duration exercise, not merely acutely, but chronically, leading to accelerated exercise and diet-induced lipolysis, and the earlier actuation and facilitation of ketogenesis.

The IMC Emergency Lipolysis Protocol



In many scenarios, where a traditional Low Carb Diet, or Zero-Carbohydrate Ketogenic Diet do not burn fat *fast* enough, it may be necessary to experiment with advanced fasting protocols to reach lipolytic goals, and this is where Intermittent Ketogenic Fasting comes into play.

Whether you like it or not, you will lose muscle during a fast as protein synthesis is a needy biological mistress. To sit at home and expect your metabolism to function superoptimally during starvation is foolish as our bodies were designed to move—to exercise, and when I say exercise I refer to *cardiovascular exercise*, for only cardiovascular exercise will maximally stimulate lipolysis through mitochondrial biogenesis, glycogen depletion, PGC1a expression, and AMPK activation. During certain periods of your fasted cardiovascular training, you will feel as though you have reached a

wall, this is a sign your glycogen levels and neurotransmitter levels are depleting, or depleted, it is a good sign, you must push past this point to reach your goals.

My ideal combined diet & exercise protocol for rapid lipolysis is as described:

- The first Four Weeks are composed of Intermittent Fasting; 24h Fasting-24h Low Fat Zero-K Refeeding-72h Weekend Fasting, with mandatory lower body MAECO Training every day: 60 Minutes at 60% Max Heart Rate Steady-state Cardio in the Morning, Afternoon, & Evening, totaling 180 Minutes per day. Warmups should be performed for the upper-body and lower muscles to prevent rapid atrophy at the very least once a week, preferably on the weekend. It is suggested that you alternate cardio exercises every workout (Incline Treadmill, Stairmaster, Bicycle, Recumbent Bike, et cetera) to reduce the inherent difficulty of training under glycogen depletion, and increase total lower body glycogen depletion through the activation of different muscle tissue. During your Zero-Carbohydrate Ketogenic Refeeding days you should only consume lean meats, and only use *MCT oil as your food oil, to ensure the mitochondria are fueled properly. Do not refeed with whole fat cheeses, fatty meats, or by adding copious amounts of vegetable or seed oils to your meals or you will dampen the process of lipolysis through enhancing intramuscular lipid accumulation, thereby decelerating subcutaneous lipolysis. Furthermore, you should consume 2-3 Tablespoons of White Distilled Vinegar each meal, ensuring that you wash out your mouth rapidly upon finishing eating with Baking Soda to prevent tooth erosion.
- The Fifth week (not pictured) will be a recovery week where you follow Time-Restricted Eating by consuming one meal a day; High protein (lean meats), low carbohydrate (slow digesting carbs, preferably dark red kidney beans), and moderate fat (one-two tablespoons of MCT oil), and allow your leg muscles ample time to regenerate through detraining. Because the goal here is not merely the promotion of health, but instead the promotion of rapid lipolysis, you should avoid consuming Linoleic acid, and especially Oleic acid and Palmitic acid until you reach your ideal scale number, but it never wise to avoid Linoleic acid use for longer than two months, in my opinion. Ensure during the recovery week you replenish sweat loss nutrients such as Sodium, Potassium Chloride, Zinc, B-Vitamins, Calcium, & Magnesium.
- It is true that your pancreas will become inflamed during this extended ketogenic diet, but there is a price to pay for everything, and the damage done should be relatively minor. You must also remember this is an emergency use protocol, not to be used for extended periods of time, as I do not personally believe combining fasting, ketogenic dieting, and endurance training is optimal for health due to the severe weight loss that will result.
- Repeat the cycle until you reach your weight loss goals.
- Unfortunately, because of the high volume and high frequency of endurance training, you will overtrain your leg muscles, but this damage can be reversed

when you return to a normal diet that is high protein (including GlySer) and train them with Regular-speed or ET:SS resistance training, giving them adequately long recovery periods of 96h+ hours between workouts, to effectively regenerate lost muscle tissue.

- Finally, if you have access to thermal therapies, consider utilizing both AM Hyperthermia Therapy, and PM Hypothermia Therapy. Although both will increase ROS and Caspase-3, this may very well result in the destruction of a certain proportion of adipocytes. Promoting adipocyte cell death is obviously not a healthy choice for an already lean individual (less adipocytes = greater risk of hyperglycemia / hyperlipidemia), or for an individual who overeats, but it will benefit those who are obese and intend on maintaining a healthy diet for the rest of their lives.

*Although Coconut oil may promote the browning of fat, or an accelerated entry into Ketosis, Lauric acid is an energy dense lipid and may perturb lipolysis to a small or large extent depending on how much is consumed with each meal, to avoid this complexity, only MCT oil is permitted to be added to each meal.

Note: Do not attempt this protocol without first consulting with a licensed medical professional, and do not attempt this protocol if you *neglect* or *skip* your cardiovascular exercise as in my view you will lose an excessive amount of muscle mass by the end of a fasting protocol if you choose to be inactive during starvation. Remember, muscles can regenerate in the absence of anabolic amino acids and fatty acids, but they will only atrophy during disuse.

"Calories" Do Not Exist

The idea of calories has always puzzled me as to equate the digestion and utilization of amino acids as similar to glucose, or dietary fat, is ludicrous. Depending on the hormonal balance, the amount of muscle mass, the proportion of fast or slow twitch muscle fiber types in our body, or other metabolic variables, the digestion and resultant adipogenic effects of a meal rich in one or more macronutrients will be different depending on a person's health and activity level.

A professional endurance athlete or sprinter will clearly digest and utilize a meal rich in carbohydrates better than a powerlifter, or bodybuilder. And an endurance athlete will clearly digest and utilize a meal rich in fatty acids better than a professional sprinter. Whereas for a sedentary individual, a meal high in one or both of the previously mentioned macronutrients will result in a much greater postprandial adipogenic effect due to pronounced metabolic and physiological differences.

Furthermore, different carbohydrate molecules stimulate insulin to different degrees, and digest at different rates, such that beta-glucans[1] found in oat & barley will not raise blood glucose or spike insulin as much as the potato starch molecule amylopectin[2].

Carbohydrate rich foods must therefore continue to be separated further by not just the current classifications of "Fast" vs "Slow" digesting, or more accurately "High Glycemic" vs "Low Glycemic" index, but in my ideal view "High Adipogenic Propensity" vs "Low Adipogenic Propensity".

Although I do not believe in calories, it is still useful to attempt to quantify the energetic burden of food and drink. We should therefore categorize the caloric value of different dietary macronutrients by the adipogenic propensity of the aforementioned macronutrients (once digested) i.e. a greater adipogenic propensity = a greater caloric value.

Clearly if you eat only plain oatmeal all day you will grow less fat than if you drink only liquid high fructose corn syrup all day, even if the "calories" contained within the liquid sugar drink are far less than the accumulated calories of the plain oatmeal, thus proving how flawed our current understanding of calories are.

No longer is it accurate or intelligent to suggest that during a bulking phase one should simply "eat more calories" i.e. eat any and all food, as certain calories will lead to faster health deterioration, and more importantly, muscle toxicity, beyond adipogenesis. Adipogenesis, if sought after, should be safely promoted in lean individuals through the increased consumption of healthy macronutrients, such as slower digesting carbohydrates, protein, and predominantly essential fats.

IMC Caloric Reimagining

(These are not completely accurate caloric measurements due to different carbohydrate profiles of foods; they have been simplified)

Per Gram of Macronutrient:

- Lean Meat Protein (Slow digesting protein) (+MCT / ALA) = **two calories**.
- Essential Fatty Acids (EF) = **five calories**.
- Non-essential Fatty Acids (+Protein Powders, excluding Palmitic acid) (NEF) = **eight calories**.
- Slow Digesting (High in Amylose, Beta-glucan, Cellulose, Pectin) Carbohydrates = **eleven calories**.
- Fast Digesting (High in Amylopectin, Dextrin, Low in fiber) Carbohydrates & Palmitic acid = **fourteen calories.**
- Liquid Sucrose = **seventeen calories.**
- Liquid Fructose = **twenty-three calories.**

Adipogenic Propensity = The Glycemic Index combined with a novel Insulinemic Index, and digestion rate times.

HAP = High Adipogenic Propensity, MAP = Moderate Adipogenic Propensity, LAP = Low Adipogenic Propensity, ELAP = Extremely Low Adipogenic Propensity.

Old Measurement: 5.3oz Potato (HAP): 26g of Carbohydrates = 104 Calories.
New Measurement: 5.3oz Potato (HAP): 26g of Carbohydrates = **364 Calories.**
Old Measurement: 1cup Oatmeal (LAP): 21.9g Carbohydrates = 87.6 Calories.
New Measurement: 1cup Oatmeal (LAP): 21.9g Carbohydrates = **240.9 Calories.**
Old Measurement: 4oz 100% Lean Beef (ELAP): 26g of Protein = 220 Calories.
New Measurement: 4oz 100% Lean Beef (ELAP): 26g of Protein = **52 Calories.**
Old Measurement: 1tbsp Linoleic acid (LAP): 14g EF = 126 Calories.
New Measurement: 1tbsp Linoleic acid (LAP): 14g EF = **70 Calories.**
Old Measurement: 1tbsp Palmitic acid (MAP): 14g NEF = 126 Calories.
New Measurement: 1tbsp Palmitic acid (MAP): 14g NEF = **196 Calories.**

Note: I do not believe we will ever be able to quantify food energy as static numbers, as every human body digests macronutrients differently, but the list above was formulated by me to provide a more accurate representation of the energy burden of different types of common foods and should help you diet more effectively.

As for Caloric Restriction, if you do not like the Zero-Carb Ketogenic Diet, and if you track your macronutrient intake, instead of looking at a specific but vague number of calories to not surpass each day during a diet (such as 1000), consider progressively restricting firstly your dietary carbohydrates, and if they are eliminated completely and you are still not lean, begin restricting fatty acids until you reach your ideal bodyfat level. Restricting protein consumption through extended dieting is adding a dangerous variable to the equation, considering you will likely not know if the weight you are losing every successive month is primarily fat or primarily muscle. The misguided and antiquated thought that all macronutrients are equal in adipogenic propensity must be extinguished, especially among the elderly, or they will continue to unknowingly accelerate their musculoskeletal decay.

[1] "<>To determine the effect of oat β-glucan (OBG) on acute glucose and insulin responses and identify significant effect modifiers we searched the MEDLINE, EMBASE, and Cochrane databases through October 27, 2020 for acute, crossover, controlled feeding trials investigating the effect of adding OBG (concentrate or oat-bran) to carbohydrate-containing test-meals compared to comparable or different carbohydrate-matched control-meals in humans regardless of health status. The primary outcome was glucose incremental area-under-the-curve (iAUC). Secondary outcomes were insulin iAUC, and glucose and insulin incremental peak-rise (iPeak). Two reviewers extracted the data and assessed risk-of-bias and certainty-of-evidence (GRADE). Data were pooled using generic inverse-variance with random-effects model and expressed as ratio-of-means with [95% CIs]. We included 103 trial comparisons (N = 538).

<>OBG reduced glucose iAUC and iPeak by 23% (0.77 [0.74, 0.81]) and 28% (0.72 [0.64, 0.76]) and insulin by 22% (0.78 [0.72, 0.85]) and 24% (0.76 [0.65, 0.88]), respectively. Dose, molecular-weight, and comparator were significant effect modifiers of glucose iAUC and iPeak. Significant linear dose-response relationships were observed for all outcomes. OBG molecular-weight >300 kg/mol significantly reduced glucose iAUC and iPeak, whereas molecular-weight <300 kg/mol did not. Reductions in glucose iAUC (27 vs 20%, p = 0.03) and iPeak (39 vs 25%, p < 0.01) were significantly larger with different vs comparable control-meals. Outcomes were similar in participants with and without diabetes. All outcomes had high certainty-of-evidence.
<>In conclusion, current evidence indicates that adding OBG to carbohydrate-containing meals reduces glycaemic and insulinaemic responses. However, the magnitude of glucose reduction depends on OBG dose, molecular-weight, and the comparator."[417.01]

[2] "<>Starches that are high in amylopectin are digested and absorbed more quickly than starches with a high amylose content and produce insulin resistance in rats during long-term feeding.
<>The aim of this study was to determine whether amylopectin-induced insulin resistance could be prevented or reversed by a period of high amylose feeding. We employed a randomized design in which two groups of rats were fed either the high amylose and then the high amylopectin diet for two consecutive 8-wk periods or vice versa (high amylopectin and then high amylose). Four other groups were fed either a high amylose or a high amylopectin diet for 8 or 16 wk. All rats were fed two 10-g meals per day (300 kJ/d), and insulin sensitivity was assessed by intravenous glucose tolerance test (IVGTT) after 8 or 16 wk of feeding.
<>We found no difference in glucose tolerance between any group at any time point. Insulin responses, however, were 50% higher (P < 0.01) after 16 wk of high amylopectin feeding [area under the plasma insulin curve (AUC) = 18.1 +/- 1.4 nmol.L-1 x 15 min] compared with high amylose feeding (AUC = 13.0 +/- 1.2 nmol.L-1 x 15 min). The two groups which received both diets developed a similar degree of insulin resistance, equivalent to that after 16 wk of high amylopectin feeding.
<>The findings suggest that amylopectin-induced insulin resistance cannot be reversed or prevented by either a subsequent or previous period of amylose feeding. Taken together, the data suggest that the nature of starch in the Western diet influences the development of noninsulin-dependent diabetes mellitus in humans."[417.02]

Caloric Restriction as it is currently scientifically described should be scientifically renamed more accurately as *Carbohydrate Restriction* in my opinion, as most studies involving Caloric Restriction merely restrict carbohydrates. Whereas antiquated Caloric Restriction should be considered *Protein Restriction*, which is a far more dangerous diet to the musculoskeletal health of the elderly. Interestingly, the more you exercise, and the more muscle mass you accrue, the less of a danger protein restriction poses, whereas for

those who exercise little, protein restriction only results in the accelerated loss of muscle mass during natural aging.

Here is a paper explaining the illogicality of a classic “calorie” in scientific terms:

“<>According to Albert Einstein, "Classical thermodynamics...is the only physical theory of universal content concerning which I am convinced that, within the framework of applicability of its basic concepts, will never be overthrown." Indeed, the first law of thermodynamics describes one of the most important principles related to body weight. The basic tenet states that energy cannot be created or destroyed but can be transformed from one form to another. The first law of thermodynamics can be written as follows:

$$\Delta E = q - w$$

<>where ΔE is the change in energy stores during any process, q is the heat produced during the process, and w is the work. The energy balance equation dictates that the energy potential of body mass remains constant when caloric intake equals caloric expenditure. Simply stated,

Change in energy stores = energy intake - energy expenditure

<>As discussed by Feinman and co-workers, although this principle always applies, the application of this law within living organisms is not simple. Strictly speaking, as written, the above mentioned equation only applies to closed systems that are close to equilibrium and that do not carry out chemical reactions. If matter can be exchanged between system and surroundings, then the system is an open one. In fact, all living organisms are open systems. Life forms take in food from the environment and use it to maintain body temperature and to run the biochemical pathways of its body. Obviously, living organisms are also far from equilibrium. The second law of thermodynamics also must be considered. The second law tells us that processes always go in the direction of randomness, or disorder (entropy). Whenever energy is exchanged, the efficiency will be imperfect, and some energy will escape – usually in the form of heat – thus increasing entropy in the universe. Importantly, the metabolic pathways that macronutrients follow may be very different due to the differences in hormonal state and enzymatic activity. <>The hormonal changes associated with a low-carbohydrate diet include a reduction in the circulating levels of insulin along with increased levels of glucagons, leading to activation of phosphoenolpyruvate carboxykinase, fructose 1,6-biphosphatase, and glucose 6-phosphatase and inhibition of pyruvate kinase, 6-phosphofructo-1-kinase, and hexokinase, favoring gluconeogenesis over glycolysis. Gluconeogenesis is an energy-consuming process as 6 mol of ATP are consumed for the synthesis of 1 mol of glucose from pyruvate or lactate. The transformation of gluconeogenic amino acids into glucose requires even more energy because ATP is needed to dispose of the nitrogen as urea. Further, a low-carbohydrate diet increases turnover of body proteins; and the energy-

dependent processes of maintaining the turnover of proteins, including synthesis, folding, targeting, regulatory processes, and protein breakdown have an overall cost to body energy homeostasis that is significantly higher than previously appreciated."[417.03]

Fasting

Fasting, or more accurately described as starvation, or Methionine and Cysteine restriction [See: Pro-Inflammation Cycle Diet], is an effective way to promote lipolysis without complication, most especially in individuals with larger amounts of muscle mass and greater muscle conditioning. It is not suggested that individuals engage in extended fasting (72h+) who suffer from weak muscles, as hypoproteinemia will only accelerate muscle atrophy, resulting in reduced health resilience over time. But for individuals who are obese, who have dispensable amounts of muscle mass, there is no quicker way to burn fat then through prolonged fasting combined with high duration cardiovascular exercise. I will clarify that I believe Prolonged Fasting should be treated as an "all-or-nothing" emergency method to rapidly accelerate lipolysis, or destroy cancer cells.

Intermittent Fasting (IF: One day eating, One day refeeding) and Time-Restricted Feeding (TR: One meal a day) have exaggerated efficacy towards promoting lipolysis and lifespan in my opinion, as the research regarding their use fail to understand that they are merely weaker variations of caloric restriction—the restriction of macronutrients, of primarily carbohydrates. To elaborate further, as overfeeding often occurs in human IF / TR diets, this mitigates the metabolic and antiaging benefits of the diets, whereas in Caloric Restriction diets, especially in mice, the risk of overfeeding is non-existent. Furthermore, the early physiological response to starvation is proteolysis, making IF hypothetically more catabolic than prolonged fasting, caloric restriction, or TR diets, but this does not mean Intermittent Fasting has no benefits as it will still promote angiogenesis in the myocardium, brain, and *skeletal muscles*[C-C2]-[See also: Pro-Inflammation Cycle Diet], and it will magnify exercise-induced muscular and neuronal autophagy.

Of note, engaging in frequent and intense glycogen depleting cardiovascular exercise will likely mitigate the early (72-96h) fasting-induced proteolysis due to the increased production of ketones. Reading on, you will learn that after fourteen days of a Ketogenic Diet, the pancreas begins to experience damage, meaning that it is unwise to exceed two weeks of zero-calorie fasting.

Substrate competition is one explanation for the glucose intolerance that develops after a prolonged fast and occurs upon refeeding with large amounts of carbohydrates and fatty acids. Our cells have trouble switching between different types of fuel sources, and this could be because of fasting-induced intestinal florae changes.

[A] 10-Days Fasting burns fat by enhancing inflammation (macrophage infiltration) in Adipose Tissue (AT), and systemic inflammation.

"<>We performed a 10-day zero-calorie inpatient fast in humans. In a subset of the subjects, we conducted serial subcutaneous AT biopsies from the periumbilical region. The participants uniformly lost weight over the course of the fast (mean = 7.2 ± 0.8 kg, max = 8.4 kg, min = 6.1 kg) coincident with the contraction of fat mass as measured by dual energy X-ray absorptiometry (DXA)."
"<>Given evidence of a macrophage gene signature in AT with fasting, we considered the possibility that this might be partially attributable to increased numbers of monocytes/macrophages. To test this, we performed a histological analysis. As the amount of available tissue was limited for standard histology and immunostaining, we imaged ultrathin sections by transmission electron microscopy (TEM).
<>We scanned the entire section, capturing TEM images of any observable cells interspersed between adipocytes, and then a blinded observer reviewed the images and identified cells that exhibited stereotypical features consistent with monocytes or macrophages. Because there was stochastic variability in the total area of the AT sections, we also counted the total number of adipocytes in the section to which we normalized the number of monocytes/macrophages.
<>After 10 days of fasting, the AT biopsy specimens revealed a significant increase ($p = 0.02$) in the frequency of interstitial cells exhibiting a monocytic or macrophage morphology. In addition, some of the cells demonstrated intracellular vesicles that stained darkly with osmium tetroxide consistent with lipid containing lysosomes or lipid droplets. These data suggest that the increase in macrophage-specific transcripts could be partially attributable to an increase in the number of macrophages with fasting either due to increased monocyte recruitment or local proliferation."
"<>We next examined additional systemic inflammatory mediators by measuring the levels of select canonical macrophage-derived cytokines by ELISA, including IL-10, IL-6, TNFα, and CCL2/MCP-1. Transcripts for each of these cytokines in AT also either increased or trended upward with fasting (IL-10: log2fold = 2.1, p = 3.64e-17, adjusted p = 1.08e-14; TNFα: log2fold = 0.81, p = 0.03, adjusted p = 0.11; IL-6: log2fold = 0.65, p = 0.09, adjusted p = 0.25; and CCL2: log2fold = 1.17, p = 0.051, adjusted p = 0.16). We performed ELISA on serum samples from baseline and day 10 of fasting, as serum was limited from the intermediate fasting time points. IL-10, IL-6, and TNFα significantly increased in the circulation at the end of the fast"
"<>To test whether there was rapid resolution of systemic inflammatory markers with refeeding, we measured CRP in samples collected the day after refeeding. We did not have sufficient serum available to measure CRP in all of the subjects at the refeeding time point as had been done for the serial fasting time points in Figure 5A; however, we did have plasma samples available and measured the CRP levels after refeeding, with paired plasma at baseline and at completion of the prolonged fast. ELISA analysis confirmed the increase in CRP with prolonged fasting with no significant reduction at the one-day refeeding time point. Collectively, these data support the concept that prolonged fasting drives metabolic inflammation."[417.A]

[B] The primary question most people, including myself have asked is how much muscle tissue is broken down into fuel during extended fasting? Interestingly, the earliest

physiological response to fasting is increased proteolysis i.e. muscle catabolism, which is when muscle fibers are broken down into amino acids, which are recycled in the body to maintain protein synthesis to keep the brain alive. Whereas the longer the fast, or shall we say, the point in time at which the body enters into ketosis, the less muscle mass is lost during a fast. This means that cardiovascular exercise is an essential albeit underutilized component of any fasting protocol to expedite the bodies entry into ketosis, which is especially important during the earliest days of a programmed prolonged fast to suppress proteolysis, and to maintain a high level of ketogenesis through enhancing basal lipolysis.

"<>Background: Fasting is attracting an increasing interest as a potential strategy for managing diseases, including metabolic disorders and complementary cancer therapy. Despite concerns of clinicians regarding protein catabolism and muscle loss, evidence-based clinical data in response to long-term fasting in healthy humans are scarce. The objective of this study was to measure clinical constants, metabolic, and muscular response in healthy men during and after a 10 day fast combined with a physical activity program.
<>Methods: Sixteen men (44 ± 14 years; 26.2 ± 0.9 kg/m2) fasted with a supplement of 200-250 kcal/day and up to 3 h daily low-intensity physical activity according to the peer-reviewed Buchinger Wilhelmi protocol. Changes in body weight (BW) and composition, basal metabolic rate (BMR), physical activity, muscle strength and function, protein utilization, inflammatory, and metabolic status were assessed during the 10 day fast, the 4 days of food reintroduction, and at 3 month follow-up.
<>Results: The 10 day fast decreased BW by 7% (-5.9 ± 0.2 kg, $P < 0.001$) and BMR by 12% ($P < 0.01$). Fat mass and lean soft tissues (LST) accounted for about 40% and 60% of weight loss, respectively, -2.3 ± 0.18 kg and -3.53 ± 0.13 kg, $P < 0.001$. LST loss was explained by the reduction in extracellular water (44%), muscle and liver glycogen and associated water (14%), and metabolic active lean tissue (42%). Plasma 3-methyl-histidine increased until Day 5 of fasting and then decreased, suggesting that protein sparing might follow early proteolysis. Daily steps count increased by 60% ($P < 0.001$) during the fasting period. Strength was maintained in non-weight-bearing muscles and increased in weight-bearing muscles (+33%, $P < 0.001$). Glycaemia, insulinemia, blood lipids, and blood pressure dropped during the fast ($P < 0.05$ for all), while non-esterified fatty acids and urinary beta-hydroxybutyrate increased ($P < 0.01$ for both). After a transient reduction, inflammatory cytokines returned to baseline at Day 10 of fasting, and LST were still lower than baseline values (-2.3% and -3.2%, respectively; $P < 0.05$ for both).
<>Conclusions: A 10 day fast appears safe in healthy humans. Protein loss occurs in early fast but decreases as ketogenesis increases. Fasting combined with physical activity does not negatively impact muscle function. Future studies will need to confirm these first findings."[417.B]

[C] Fasting promotes angiogenesis, and more impressively, angiogenic *efficiency*, in the ischemic (hypoxically injured) brain. Surely this study illustrates the high probability of

fasting being capable of magnifying endurance exercise-induced brain angiogenesis. For this research applied intelligently, See: IMC Workout Protocols: Angio-Fast.

"<>Background/Aims: Prolonged fasting (PF) was shown to be of great potency to promote optimal health and reduce the risk of many chronic diseases. This study sought to determine the effect of PF on the endothelial progenitor cell (EPC)-mediated angiogenesis in the ischemic brain and cerebral ischemic injury in mice. <>Methods: Mice were subjected to PF or periodic PF after cerebral ischemia, and histological analysis and behavioral tests were performed. Mouse EPCs were isolated and examined, and the effects of EPC transplantation on cerebral ischemic injury were investigated in mice.
<>Results: It was found that PF significantly increased the EPC functions and angiogenesis in the ischemic brain, and attenuated the cerebral ischemic injury in mice that was previously subjected to cerebral ischemia. Periodic PF might reduce cortical atrophy and improve long-term neurobehavioral outcomes after cerebral ischemia in mice. The eNOS and MnSOD expression and intracellular NO level were increased, and TSP-2 expression and intracellular O2- level were reduced in EPCs from PF-treated mice compared to control. In addition, transplanted EPCs might home into ischemic brain, and the EPCs from PF-treated mice had a stronger ability to promote angiogenesis in ischemic brain and reduce cerebral ischemic injury compared to the EPCs from control mice. The EPC-conditioned media from PF-treated mice exerted a stronger effect on cerebral ischemic injury reduction compared to that from control mice.
<>Conclusion: Prolonged fasting promoted EPC-mediated ischemic angiogenesis and improved long-term stroke outcomes in mice. It is implied that prolonged fasting might potentially be an option to treat ischemic vascular diseases."[417.C]
[C2] Intermittent Fasting (24h) promotes lipolysis through enhanced VEGF expression in white adipose tissue, further illustrating the *inflammatory* benefits of fasting.

"<>Intermittent fasting (IF), a periodic energy restriction, has been shown to provide health benefits equivalent to prolonged fasting or caloric restriction. However, our understanding of the underlying mechanisms of IF-mediated metabolic benefits is limited. Here we show that isocaloric IF improves metabolic homeostasis against diet-induced obesity and metabolic dysfunction primarily through adipose thermogenesis in mice.
<>IF-induced metabolic benefits require fasting-mediated increases of vascular endothelial growth factor (VEGF) expression in white adipose tissue (WAT). Furthermore, periodic adipose-VEGF overexpression could recapitulate the metabolic improvement of IF in non-fasted animals. Importantly, fasting and adipose-VEGF induce alternative activation of adipose macrophage, which is critical for thermogenesis. Human adipose gene analysis further revealed a positive correlation of adipose VEGF-M2 macrophage-WAT browning axis.
<>The present study uncovers the molecular mechanism of IF-mediated metabolic benefit and suggests that isocaloric IF can be a preventive and therapeutic approach against obesity and metabolic disorders."[417.C1]

[D] Research on the effects that fasting (Ramadan) has on the microbiome generally show that the ratio of Firmicute to Bacteroides decreases, alongside the rise of pathogenic bacteria. This would align with the *systemic inflammation* that occurs during prolonged fasting, and the facilitation of the lipolytic program. Although the idea of combining probiotics alongside fasting, currently called PROFAST, may have many benefits, such as anti-cancer effects, or a promotion of angiogenesis without risk of tumorigenicity, it would seem contradictory to use anti-inflammatory probiotics on a protocol designed to reduce adiposity.

Conversely, when fasting is completed and a return to normalcy occurs i.e. refeeding, it is vital to *reset* the intestinal microbiome by enhancing the growth of beneficial organisms, such as the Firmicutes, through dietary prebiotics and supplemented probiotics. If you fast chronically, and refeed with simple sugars, starches, or processed foods, in place of vibrant colorful vegetables and fermented foods, you may experience detrimental physiological effects, although research shows that the microbiome may return to baseline levels after cessation of intermittent fasting[417.D], I am not confidant that extended fasting is liable to result in the same homeostatic rejuvenation of beneficial organisms. An interesting thought to consider is that fasting, either willingly, or forced, throughout human history, and even far earlier in evolution, is likely to be considered the original and most primordial form of Inflammation Cycling.

"<>The increase in Bacteroidetes and Firmicutes abundance was a common finding, and the Firmicutes/Bacteroidetes ratio, an indicator of the microbiota associated with obesity, remained increased after Ramadan fasting. Furthermore, changes in the microbiota seemed to be related to ethnicity. Thus, Proteobacteria were enriched after fasting, possibly due to a significantly higher abundance of Klebsiella, whereas Bacteroidetes were more prevalent among Chinese individuals before fasting. Firmicutes were significantly more abundant among Pakistani subjects prior to fasting, while Bacteroidetes were significantly more prevalent after fasting.
<>The compositional changes in gut microbiota following the end of the Ramadan fasting are highlighted by the results of the studies included in our analysis. Ramadan fasting significantly increased some taxa (Bacteroides, Butyricicoccus, Eubacterium, Faecalibacterium, and Roseburia), which are altered in obesity. However, the exact relationship between these genera and obesity is still not fully understood. These compositional changes primarily involve an increase in butyrate-producing bacteria, which could be interpreted as a trend toward a balanced gut microbiota.
<>After Ramadan fasting, the total bacterial count and number of Bifidobacterium and Lactobacillus species decreased significantly in fecal samples from nine healthy volunteers. Understanding the underlying mechanisms of these changes and their implications for human health requires additional research."[417.E]

[E] Prolonged Fasting may result in a rebound upregulation of neurogenic and physiological adipogenic processes in the body during refeeding, making it necessary to not consume a large amount of non-essential fats or carbohydrates when refeeding. I believe the downregulated of the Pomc gene relates to appetite and may cause overeating,

whereas the reduced fat oxidation upon refeeding is clearly due to substrate competition and increased carbohydrate consumption.

"<>To endure prolonged fasting, animals undergo important acute physiological adjustments. However, whether severe fasting also leads to long-term metabolic adaptations is largely unknown. Forty-eight-hour fasting caused a pronounced weight loss in adult C57BL/6 male mice. Seven days of refeeding increased body adiposity to levels above baseline, whereas fasting-induced reductions in lean body mass and energy expenditure were not fully recovered. Respiratory exchange ratio and locomotor activity also remained altered. A fasting/refeeding cycle led to persistent suppression of Pomc mRNA levels and significant changes in the expression of histone deacetylases and DNA methyltransferases in the hypothalamus.
<>Additionally, histone acetylation in the ventromedial nucleus of the hypothalamus was reduced by prolonged fasting and remained suppressed after refeeding. Mice subjected to 48-h fasting 30 days earlier exhibited higher body weight and fat mass compared to aged-matched animals that were never food-deprived.
<>Furthermore, a previous fasting experience altered the changes in body weight, lean mass, energy expenditure and locomotor activity induced by a second cycle of fasting and refeeding. Notably, when acutely exposed to high-palatable/high-fat diet, mice that went through cumulative fasting episodes presented higher calorie intake and reduced energy expenditure and fat oxidation, compared to mice that had never been subjected to fasting.
<>When chronically exposed to high-fat diet, mice that experienced cumulative fasting episodes showed higher gain of body and fat mass and reduced energy expenditure and calorie intake. In summary, cumulative episodes of prolonged fasting lead to hypothalamic epigenetic changes and long-lasting metabolic adaptations in mice."[417.F]

[E2] Another study detailing why Prolonged Fasting results in glucose intolerance and hyperinsulinemia during refeeding (pathologically increased Free Fatty Acids).

"<>The aim of this study was to establish the experimental paradigm of fasting, followed by refeeding, to investigate individual differences in nutrient partitioning. Eight nonobese men were fed a normal meal (25% of daily energy requirements) on two occasions, after an overnight (13-h) fast and after a prolonged (72-h) fast. During the entire fasting period, subjects were resident in a whole room indirect calorimeter, and blood samples were drawn periodically. Because no other food was consumed over the 12 h after either meal, negative energy balance was observed after the overnight and prolonged fast.
<>Postprandial carbohydrate oxidation was significantly reduced after the 72- vs. 13-h fast ($P < 0.0001$), whereas fat oxidation was significantly increased ($P < 0.0001$). Interestingly, carbohydrate balance was positive after the prolonged fast but negative after the overnight fast (24 +/- 17 vs. -57 +/- 16 g/12 h, respectively; $P < 0.001$), whereas fat balance was negative under both conditions (-78 +/- 7 vs. -47 +/- 8 g/12 h, respectively; $P < 0.002$).
<>With 72 h of fasting, the glucose and insulin excursions in response to the mixed meal were significantly greater compared with the 13-h fast ($P < 0.001$). In conclusion,

prolonged fasting resulted in a significant decrease in carbohydrate oxidation and an increase in fat oxidation, after a normal mixed meal, in healthy men. This was associated with a significant decrease in glucose tolerance. Because circulating free fatty acids were greatly elevated at all times after the prolonged fast, these may be mediating some of the changes in postprandial metabolism."[417.F1]

[F] Fasting enhances lifespan through multiple mechanisms, the primary being an obvious decrease in mTOR expression, but another mechanism is the increased production of endogenous fatty acid amines such as Palmitoylethanolamide, a PPAR receptor agonist, See: Myokines, and the polyamine Spermidine, See: Pro-Inflammation Cycle Supplementation: L-Ornithine.

"<>Background: Periodic prolonged fasting (PF) extends lifespan in model organisms and ameliorates multiple disease states both clinically and experimentally owing, in part, to its ability to modulate the immune system. However, the relationship between metabolic factors, immunity, and longevity during PF remains poorly characterized especially in humans.
<>Objective: This study aimed to observe the effects of PF in human subjects on the clinical and experimental markers of metabolic and immune health and uncover underlying plasma-borne factors that may be responsible for these effects.
<>Methods: In this rigorously controlled pilot study (ClinicalTrial.gov identifier, NCT03487679), 20 young males and females participated in a 3-d study protocol including assessments of 4 distinct metabolic states: 1) overnight fasted baseline state, 2) 2-h postprandial fed state, 3) 36-h fasted state, and 4) final 2-h postprandial re-fed state 12 h after the 36-h fasting period. Clinical and experimental markers of immune and metabolic health were assessed for each state along with comprehensive metabolomic profiling of participant plasma. Bioactive metabolites identified to be upregulated in circulation after 36 h of fasting were then assessed for their ability to mimic the effects of fasting in isolated human macrophage as well as the ability to extend lifespan in Caenorhabditis elegans.
<>Results: We showed that PF robustly altered the plasma metabolome and conferred beneficial immunomodulatory effects on human macrophages. We also identified 4 bioactive metabolites that were upregulated during PF (spermidine, 1-methylnicotinamide, palmitoylethanolamide, and oleoylethanolamide) that could replicate these immunomodulatory effects. Furthermore, we found that these metabolites and their combination significantly extended the median lifespan of C. elegans by as much as 96%.
<>Conclusions: The results of this study reveal multiple functionalities and immunological pathways affected by PF in humans, identify candidates for the development of fasting mimetic compounds, and uncover targets for investigation in longevity research."[417.G]

[G] Fasting, although being neuroprotective against numerous brain insults, and promoting autophagy, is not capable of promoting amyloid breakdown, and may even

promote amyloid deposition. In dementia brains cellular apoptosis is significantly increased, which is why a sudden decrease in mTOR / AKT may very well exacerbate the neurotoxicity of the accumulation of neurological molecular waste.

"<>We developed a new technique to observe macroautophagy in the brain in vivo, and examined whether fasting induced macroautophagy in neurons and how the induction was different between Alzheimer's disease (AD) model and control mice. Lentivirus for EGFP-LC3 injected into the brain successfully visualized autophagosome in living neurons by two-photon microscopy. The time-lapse imaging revealed that fasting increased the number, size and signal intensity of autophagosome in neurons.
<>In AD model mice, these parameters of autophagosome were higher at the basal levels before starvation and increased more rapidly by fasting than in control mice. However, metabolism of exogenous labeled Aβ evaluated by the new technique suggested that the activated macroautophagy was insufficient to degrade the intracellular Aβ increased by enhanced uptake from extracellular space after fasting."
<>Our results also suggested even though autophagy was activated in 5xFAD mice under starvation, the intracellular degradation of Aβ was still insufficient to compensate [for] the increased uptake of Aβ from extracellular space. The idea was further supported by immunohistochemistry of 5xFAD mice showing that fasting treatment enhanced intracellular accumulation of endogenous Aβ. Moreover, fasting did not largely affect extracellular accumulation of endogenous Aβ in 5xFAD mice.
<>If this is the case in human AD pathology, such enhanced uptake of Aβ by calorie restriction could be harmful for neuronal function if the intracellular Aβ triggers abnormal signaling cascade. Supporting this hypothesis, we observed increased number of neurons with intracellular Aβ that lost viability after fasting treatment."[417.H]

[H] Fasting increases cortisol release (alongside overfeeding), making concurrent L-Ornithine supplementation during a prolonged fast beneficial towards at the very least reducing proteolysis, and stress hormone-induced neurotoxicity.

"<>Chronic caloric deprivation and obesity are complicated by hypercortisolemia. The effects of acute overfeeding and fasting on circulating free cortisol levels and conversion of cortisone to free cortisol are unknown. We hypothesized that serum-free cortisol and free cortisol-to-cortisone ratio would increase after both overfeeding and fasting.
<>This is a prospective study of 22 healthy volunteers who completed a 10-day high-calorie protocol followed by a 10-day fast, separated by a 2-wk washout. Morning free and total cortisol and free cortisone levels (LC/MS) were measured at baseline and after 10 days of each intervention. Both high-calorie feeding and fasting increased total and free cortisol and the free cortisol-to-free cortisone ratio ($P = 0.001$ to $P = 0.046$). There were sex interactions, with significant effects in men ($P < 0.001$), but not in women ($P = 0.898$ and 1.000, respectively) in subset analyses examining the effects of fasting on free cortisol and the free-to-total cortisol ratio.
<>Overfeeding and fasting both increase circulating free cortisol levels and appear to alter the balance between cortisol and its inactive metabolite, cortisone. Further study is

warranted to determine whether elevated cortisol levels contribute to complications of starvation and obesity, such as bone fragility.
<>NEW & NOTEWORTHY Overfeeding and fasting both increase circulating free cortisol levels and appear to alter the balance between cortisol and its inactive metabolite, cortisone. The effect of fasting on free cortisol levels is modified by sex. Further study is needed to determine the mechanisms driving the increases in cortisol."[417.I]

[I] Prolonged fasting appears to enhance intramuscular lipid accumulation in muscle tissue, while facilitating whole body fat oxidation, which likely is the body's way of providing continuous fuel to slow twitch muscle fibers for the promotion of locomotive survivalism. Although this may seem negative, earlier in the section *Muscle Lipid Accumulation* we learned that fasted chronic aerobic exercise promotes intramuscular fat breakdown, therefore it is not a derangement in metabolism that drives fasting-induced lipid accumulation, it is a compensatory mechanism our body exerts to sustain itself. Albeit prolonged fasting in sedentary individuals, or individuals who solely engage in anaerobic (strength training: fast twitch athletes) may lead to a worsening of insulin resistance due to a change in fuel source (fatty acids) and increased IM lipid accumulation. Therefore, it would make sense logically to suggest that endurance exercise always be performed on a prolonged or short duration fast to mitigate IM lipid accumulation and directly burn IM lipids.

"<>Objective: Type 2 diabetes and insulin resistance have been associated with mitochondrial dysfunction, but it is debated whether this is a primary factor in the pathogenesis of the disease. To test the concept that mitochondrial dysfunction is secondary to the development of insulin resistance, we employed the unique model of prolonged fasting in humans. Prolonged fasting is a physiologic condition in which muscular insulin resistance develops in the presence of increased free fatty acid (FFA) levels, increased fat oxidation and low glucose and insulin levels. It is therefore anticipated that skeletal muscle mitochondrial function is maintained to accommodate increased fat oxidation unless factors secondary to insulin resistance exert negative effects on mitochondrial function.
<>Research design and methods: While in a respiration chamber, twelve healthy males were subjected to a 60 h fast and a 60 h normal fed condition in a randomized crossover design. Afterward, insulin sensitivity was assessed using a hyperinsulinemic-euglycemic clamp, and mitochondrial function was quantified ex vivo in permeabilized muscle fibers using high-resolution respirometry.
<>Results: Indeed, FFA levels were increased approximately ninefold after 60 h of fasting in healthy male subjects, leading to elevated intramuscular lipid levels and decreased muscular insulin sensitivity. Despite an increase in whole-body fat oxidation, we observed an overall reduction in both coupled state 3 respiration and maximally uncoupled respiration in permeabilized skeletal muscle fibers, which could not be explained by changes in mitochondrial density.
<>Conclusions: These findings confirm that the insulin-resistant state has secondary negative effects on mitochondrial function. Given the low insulin and glucose levels after

prolonged fasting, hyperglycemia and insulin action per se can be excluded as underlying mechanisms, pointing toward elevated plasma FFA and/or intramuscular fat accumulation as possible causes for the observed reduction in mitochondrial capacity."[417.J]

[J] Prolonged Fasting, through stimulation of Ketones, and HDAC1 inhibition promotes a pro-survival change to muscle progenitor cells by causing "deep quiescence", making them resilient to damage and delaying their aging, thus explaining why studies involving Ketogenic Diets consistently result in anti-aging muscle function benefits in mice. This anti-aging effect on muscles can clearly be mimicked through the supplementation of exogenous ketones without a drastic change of diet.

"<>Dietary caloric restriction (CR) and fasting generally induce cell-protective effects in various organisms ranging from yeast to mammals. They also consistently promote lifespan and healthspan in various organisms. Although they often affect common signaling mechanisms, including sirtuins and mTOR, and cellular mechanisms, such as autophagy, how they affect upstream mechanisms, such as metabolism and substrate utilization, to control cellular homeostasis, regeneration, and aging, is not fully understood.
<>Among the major nutrients, namely glucose, protein, and fat, fat is the most prominently mobilized and used in the presence of starvation. In particular, the utilization of ketone bodies, water-soluble derivatives of fat that readily penetrate the blood-brain barrier, replaces glucose oxidation in the brain in response to fasting, which in turn spares gluconeogenesis and preserves body proteins. Increasing lines of evidence suggest that ketone bodies play an important role in mediating the salutary effects of CR and fasting.
<>In a recent paper published in Cell Metabolism, Benjamin et al. demonstrated that fasting delays muscle regeneration acutely but promotes a state of deep quiescence (DQ) characterized by downregulation of cell proliferation genes and upregulation of genes involved in stemness in muscle stem cells (MuSCs). MuSCs with DQ are highly stress-resistant and exhibit improved survival during stress. Importantly, the effect of fasting is mediated by ketosis, which can be mimicked by ketogenic diet consumption or exogenously administered β-hydroxybutyrate (BHB). BHB directly promotes MuSC DQ independently of its metabolism, namely through inhibition of HDAC1 and acetylation/activation of p53"[417.K]

[K] Fasting does promote a form of "detoxification" through activating mitophagy (autophagy). Interestingly, mitochondrial fission appears to associate with mitophagy, whereas mitochondrial fusion clearly suppresses it. This means that beneficial catabolic processes are inhibited, as expected, by anabolic processes, and that in situations of extended starvation and macronutrient deprivation, excessive autophagy can be nearly as damaging as its inverse process, unremitted anabolism (dementia, cancer growth), and senescence.

"<>Fasting in vivo and nutrient deprivation in vitro enhance sequestration of mitochondria and other organelles by autophagy for recycling of essential nutrients. Here our goal was to use a transgenic mouse strain expressing green fluorescent protein (GFP) fused to rat microtubule-associated protein-1 light chain 3 (LC3), a marker protein for autophagy, to characterize the dynamics of mitochondrial turnover by autophagy (mitophagy) in hepatocytes during nutrient deprivation. In complete growth medium, GFP-LC3 fluorescence was distributed diffusely in the cytosol and incorporated in mostly small (0.2–0.3 μm) patches in proximity to mitochondria, which likely represent preautophagic structures (PAS).
<>After nutrient deprivation plus 1 μM glucagon to simulate fasting, PAS grew into green cups (phagophores) and then rings (autophagosomes) that enveloped individual mitochondria, a process that was blocked by 3-methyladenine. Autophagic sequestration of mitochondria took place in 6.5 ± 0.4 min and often occurred coordinately with mitochondrial fission. After ring formation and apparent sequestration, mitochondria depolarized in 11.8 ± 1.4 min, as indicated by loss of tetramethylrhodamine methylester fluorescence. After ring formation, LysoTracker Red uptake, a marker of acidification, occurred gradually, becoming fully evident at 9.9 ± 1.9 min of ring formation. After acidification, GFP-LC3 fluorescence dispersed. PicoGreen labeling of mitochondrial DNA (mtDNA) showed that mtDNA was also sequestered and degraded in autophagosomes.
<>Overall, the results indicate that PAS serve as nucleation sites for mitophagy in hepatocytes during nutrient deprivation. After autophagosome formation, mitochondrial depolarization and vesicular acidification occur, and mitochondrial contents, including mtDNA, are degraded."

↓ continued

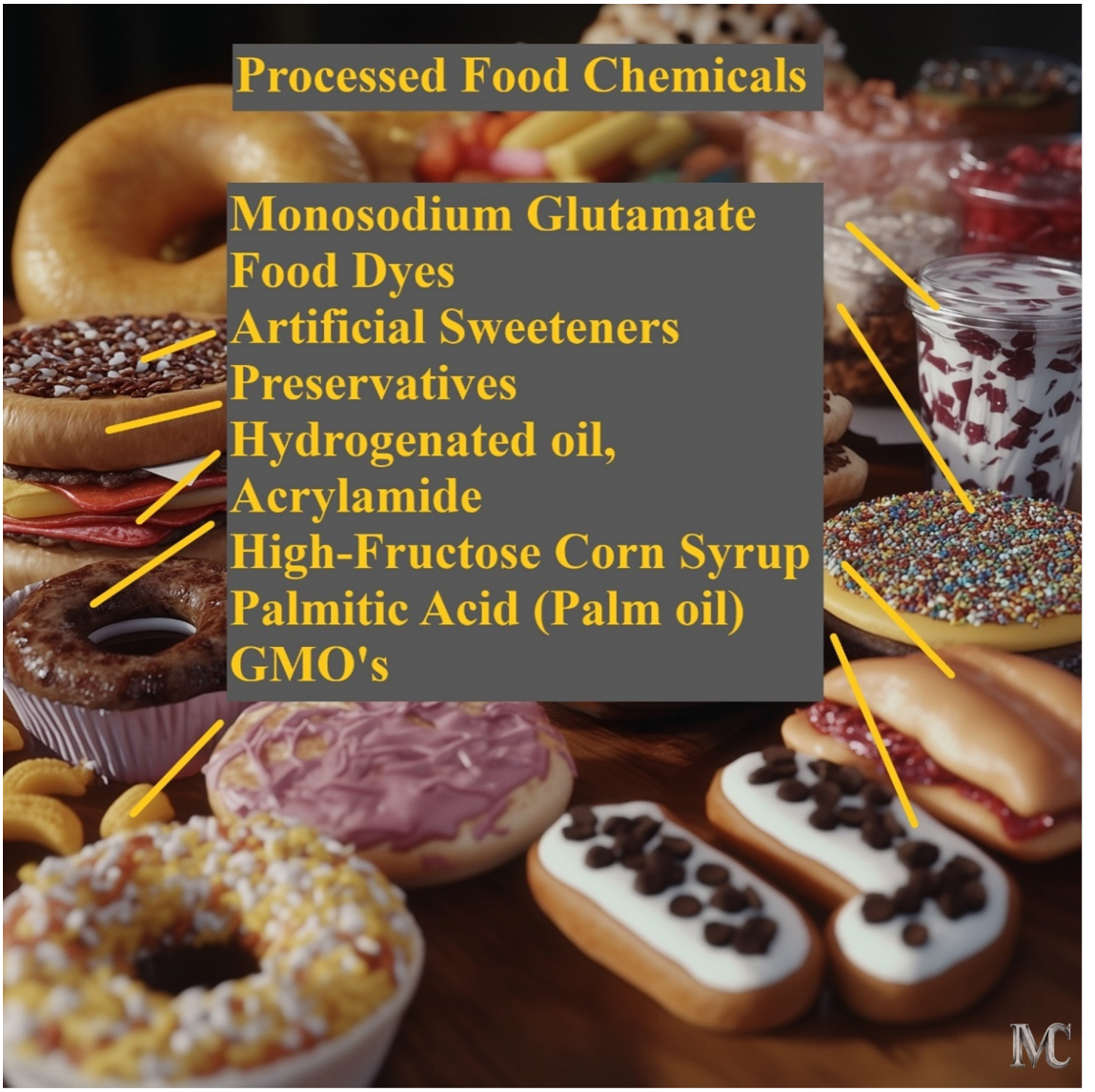
"<>In a recent report appearing after the present work was completed, mitochondrial fission and autophagy were characterized in Ins1 insulinoma cells (43). Mitochondrial fission and partial depolarization preceded mitophagy, as assessed by accumulation of MitoTracker Red-labeled mitochondria into GFP-LC3-labeled structures in the presence of protease inhibitors. Mitochondria undergoing mitophagy contained decreased optic atrophy type 1 (Opa1), a fusion-promoting protein in mitochondria. Moreover, overexpression of Opa1 and suppression of fission-1 (Fis1) or dynamin-related protein 1 (Drp1), two proteins involved in mitochondrial fission, decreased mitophagy.
<>Thus, mitochondrial fission promoted mitophagy, whereas fusion was inhibitory. However, in contrast to the present work in hepatocytes in which mitochondrial fission, depolarization, and autophagic sequestration took place in only a few minutes, mitochondrial fission and depolarization occurred hours before autophagy in Ins1 cells. This striking difference in time course may be due to differences of conditions (nutrient deprivation vs. nutrient replete incubation), cell type (hepatocytes vs. Ins1 cells), and methodologies."

↓ continued

"<>In summary, nutrient deprivation accelerated mitophagy in cultured rat hepatocytes. Since mitochondria were sequestered in 85% of autophagosomes but comprise only 20% of the volume of the cytosol, nutrient deprivation-induced autophagy would appear to

involve, at least in part, selective mitophagy. In this mitophagy, PAS first associated with polarized mitochondria and in a few minutes grew into cup-shaped phagophores that enveloped and sequestered target mitochondria in autophagic vesicles. Frequently, mitophagy occurred coordinately with mitochondria fission. Abrupt mitochondrial depolarization occurred at or following sequestration. Lastly, the fully formed mitophagosomes acidified and their contents, including mtDNA, degraded. These events provide a framework for analyzing mitophagy in disease."[417.L]

Food Neuroscience



Fat growth is generally known to be a direct result of elevated insulin levels, but there is

much more complexity to the process. Beyond overeating, it is my opinion that Palmitic acid & Fructose (High Fructose Corn Syrup) are the driving forces in the development of obesity, due to the development of Insulin Resistance, and hyperinsulinemia. Considering sugar and dietary fats alter our neuronal substrates and receptors, it is safe to say that food, especially many forms of junk food, are drugs, and therefore a danger to those who do not understand their addictive qualities. The amount of time, effort, and money junk food companies spend on developing and even bioengineering synthetic flavors to manipulate our sensory system is unknown, but it must be extremely high.

There is far more to our cravings than simply Dopaminergic signaling, there are many receptors and other neurotransmitters that become active during and after the consumption of high carbohydrate, high fat, and synthetic chemical-laden foodstuff, it may be that our cravings for unhealthy foods and drinks is a an attempt made by our brains to reach homeostasis, to quell the neurotoxicity of psychological stress, or it could simply be an unhealthy gut microbiome sending signals to our brains to feed them more of what they crave, but this is only a hypothesis of mine.
In the end, our cravings take hold of us and harm our bodies and our brains, but can we really blame large corporations for working towards making their processed food products taste better? They are profit driven after all, and if you truly care about what you eat you should learn to cook for yourself, as there is no reason to spend an obscene amount of money on premade health foods, or drinks, when you can easily prepare these macronutrient mixtures at home for less cost.

[A] Consuming Junk Food activates the AMPA Receptors in the Nucleus Accumbens, a part of the brain that promotes cue-rewards (addiction).

“<>Urges to eat are influenced by stimuli in the environment that are associated with food (food cues). Obese people are more sensitive to food cues, reporting stronger craving and consuming larger portions after food cue exposure. The nucleus accumbens (NAc) mediates cue-triggered motivational responses, and activations in the NAc triggered by food cues are stronger in people who are susceptible to obesity. This has led to the idea that alterations in NAc function similar to those underlying drug addiction may contribute to obesity, particularly in obesity-susceptible individuals.
<>Motivational responses are mediated in part by NAc AMPA receptor (AMPAR) transmission, and recent work shows that cue-triggered motivation is enhanced in obesity-susceptible rats after ‘junk-food' diet consumption. Therefore, here we determined whether NAc AMPAR expression and function is increased by ‘junk-food' diet consumption in obesity-susceptible vs -resistant populations using both outbred and selectively bred models of susceptibility. In addition, cocaine-induced locomotor activity was used as a general ‘read out' of mesolimbic function after ‘junk-food' consumption.
<>We found a sensitized locomotor response to cocaine in rats that gained weight on a ‘junk-food' diet, consistent with greater responsivity of mesolimbic circuits in obesity-susceptible groups. In addition, eating ‘junk-food' increased NAc calcium-permeable-AMPAR (CP-AMPAR) function only in obesity-susceptible rats.

<>This increase occurred rapidly, persisted for weeks after ‘junk-food' consumption ceased, and preceded the development of obesity. These data are considered in light of enhanced cue-triggered motivation and striatal function in obesity-susceptible rats and the role of NAc CP-AMPARs in enhanced motivation and addiction.”[417.1]

[B] Sleep Restriction alters the activity of discrete parts of the brain that associate with satiety and memory. Interestingly, higher fat consumption in sleep deprived subjects activates the prefrontal cortex, leading me to believe that Junk Food consumption may not only be addictive through dopaminergic activity, but also as a remedy to counteract sleep-induced decreased AMPA receptor activity.

“<>Here, we specifically explored the neuronal circuitry related to unhealthy and healthy food types during periods of restricted sleep. In line with our hypothesis, the insular cortex as well as areas thought to be involved in hedonic functions, such as the orbitofrontal cortex and dorsolateral prefrontal cortex, displayed the strongest activation in response to unhealthy food compared with healthy food stimuli, specifically during the period of restricted sleep.
<>The insula was integral to our hypothesis because of its known role in energy homeostasis, regulation of pleasure-seeking behaviors, integration of external stimuli, signal salience and internal bodily states of arousal. In the present study, the insula was activated by unhealthy foods to a greater extent than healthy foods, especially under sleep restricted states and was inversely related to food intake. Enhanced insular activation during restricted sleep is consistent with an amplification of the salience of unhealthy foods relative to healthy foods and recent reports of an inverse correlation between change in hunger after consumption of a high-fat yogurt and cerebral blood flow in the insula relative to consumption of a low-fat yogurt. Although preliminary, these results support a role for the insula as part of a regulatory mechanism encompassing the subjective emotional context responsive to signal salience and bodily state. Interestingly, in this study, when we assessed food intake on a day of ad libitum feeding before the fMRI scan, participants ate more often and ate more fat during the restricted sleep period than the habitual sleep period.
<>It is interesting to note that, in this study, the right insula was preferentially activated by unhealthy foods during restricted sleep. There has been evidence of right-sided bias for chemosensory stimuli and in gustatory imaging studies. Also, neuroimaging studies suggest that the right orbitofrontal cortex is involved in short-term memory tasks.
<>In addition to the insula, various sections of the prefrontal cortex, such as the medial frontal cortex, also displayed stronger activation in response to unhealthy as compared with healthy food stimuli. Activation of the medial frontal cortex, which is thought to be involved in higher reasoning as well as attention, suggests that unhealthy food stimuli may trigger neural responses related to high level cognitive process.
<>Unhealthy food, relative to nonfoods, elicited specific responses in the orbitofrontal cortex, a brain area known to be associated with pleasure and hedonic responses as well as the anticipation of reward. This association is corroborated by Schloegl et al., who described the orbitofrontal cortex as a hedonic control center for food.

<>The comparison of regional brain activity in response to unhealthy foods during habitual relative to restricted sleep yielded interesting results. They showed an expected advantage of sleep on neuronal responses to food stimuli, such as upregulation of some arousal areas (thalamus and precuneus), and upregulation of the cingulate gyrus suggests that a cognitive control mechanism may also be more active following habitual sleep than restricted sleep. This could possibly signify improved food restraint behavior."[417.2]

[C] High Carbohydrate meals influence serotonin synthesis, most likely through Insulin signaling, meaning that overeating is an insidious antidepressant that people utilize to improve mood.

"<>Background: The delivery of circulating tryptophan to the brain and its conversion to serotonin vary directly with plasma concentrations of tryptophan and inversely with those of other large neutral amino acids (LNAAs). Although carbohydrate-rich, protein-free formula diets have been shown to elevate, and high-protein diets to depress, the tryptophan-LNAA ratio, few data are available about this ratio's responses to actual meals.
<>Objective: We determined whether carbohydrate-rich or protein-rich breakfasts, such as those Americans normally eat, produce substantial differences in the plasma tryptophan-LNAA ratio and in the corresponding ratio for tyrosine, the precursor of brain dopamine and norepinephrine.
<>Design: Nine overnight-fasted subjects consumed, 3-7 d apart, a carbohydrate-rich (69.9 g carbohydrate and 5.2 g protein) and a protein-rich (15.4 g carbohydrate and 46.8 g protein) breakfast. Blood samples collected at baseline and after 40, 80, 120, and 240 min were assayed for tryptophan, tyrosine, the 5 other LNAAs, and insulin.
<>Results: The carbohydrate-rich and protein-rich breakfasts had significantly different effects on both the plasma tryptophan-LNAA and tyrosine-LNAA ratios (each $P < 0.01$). Among the 8 subjects who consumed both breakfasts, the median difference for tryptophan:LNAA was 54% (range: 36-88%) and for tyrosine:LNAA was 28% (range: 10-64%). Insulin concentrations rose significantly after the carbohydrate but not after the protein meal.
<>Conclusions: High-carbohydrate and high-protein breakfasts similar to those Americans normally eat can cause substantial differences in the plasma tryptophan ratio and thus, probably, in brain tryptophan concentrations and serotonin synthesis. Such meals also change the plasma tyrosine ratio and may thereby modify catecholamine synthesis."[417.3]

[D] Obese individuals who are otherwise healthy have greater olfactory sensitivity, which is normally suppressed in the process of meal satiety, leading to greater sensitivity to food odor, and therefore greater food intake. The inhalation of Essential oils may counteract this olfactory dysfunction.

"<>We expected that odor sensitivity decreases in response to food intake reflecting less need to search for nutrients in the environments as has been reliably shown in animal

models. We assumed that this mechanism may be changed by poor metabolic health, and thus insufficient modulation of central odor sensitivity in obesity. Namely, we expected that while participants with normal weight would show a significant decrease in response to meal intake, participants with obesity might show similar odor sensitivity in the hungry and sated state in accordance with most recent literature on low reactivity of sensory (odor intensity) and metabolic (ghrelin reactivity) systems in response to changing hunger states in obesity.
<>In contrast with our expectations, we detected a negative indirect effect of BMI on change in odor sensitivity through the mediator IR, meaning that the higher the BMI together with high IR, the more negative is the change in odor sensitivity. A negative change score represents a decrease in odor sensitivity, while a positive score represents an increase in odor sensitivity in the sated when compared to the fasted state. Hence, odor sensitivity for chocolate decreases in metabolically impaired individuals with a high BMI after a meal, while no change in odor sensitivity is observed in metabolically healthy participants. However, we show a positive direct effect of BMI on change in odor sensitivity for chocolate depending on hunger state independent of metabolic health parameters.
<>Thus, the effect of BMI on the change in odor sensitivity in response to a meal is positive after removing the effect of metabolic health (= adjusting for the mediators). This means that a high BMI is associated with an increase in odor sensitivity in the sated state, but only in metabolically healthy individuals. Further applied post hoc analyses underpinned this finding. We could show that participants with obesity outperformed those of normal weight while controlling for IR, but this effect was not present in the same design without IR as a covariate.
<>Thus, individuals with obesity, who are metabolically healthy might have higher sensitivity for food odors in the sated state, while people affected by high HOMA-IR values independent of body weight status show lower olfactory sensitivity for food odors. Since we find these effects in the food odor condition only, our results support the proposed idea from Riera and colleagues, that reduced olfactory input protects against intake of high caloric diet by mimicking reduced odor sensitivity after meal intake. This might also reflect a specific reaction of our sensing system to food odor cues in response to our hunger state."[417.4]

[E] Sensory-related industrial additives (SRIAs) are added to processed foods and drinks to enhance their respective taste profiles, either through changes to texture, sweetness, or other taste variables. Many SRIAs are now being linked to metabolic syndrome, and obesity. For a complete list of the major SRIAs see [417.6].

"<>Background: Increasing evidence suggests that ultra-processed foods (UPFs) lead to elevated risk of obesity-related conditions, but UPF measurement has been criticized for its subjectivity and lack of clarity on biological mechanism. Sensory-related industrial additives (SRIAs) are a defining feature of UPFs and may encourage overconsumption by enhancing the sensory quality of foods. However, practical challenges have prevented systematic incorporation of SRIAs into UPF measurement.

<>Objective: The objectives of this work were to describe a new, open-source ingredient list search method and to apply this method to describe the presence of SRIAs in US packaged foods. Methods: We developed computer coding to search for 64 common SRIAs related to sweetness, flavor, appearance, and texture in 241,688 foods in the US Branded Food Products Database (BFPD). The BFPD includes manufacturer-provided ingredient lists for ~300,000 branded and private label food items. We determined the total number of SRIAs (0-64) and the number of different types of SRIAs (sweetness, flavor, appearance, texture, 0-4) in each food, then calculated the percent of all foods with SRIAs. This was done for all foods, and by food group for 224,098 items with food group data.
<>Results: Most (64.9%) foods in the BFPD contained at least one SRIA, and more than a third had at least three. Sweets (89.5%), beverages (84.9%), and ready-to-eat (RTE) foods (82.0%) were the most likely to contain SRIAs. With respect to SRIA types, 25.7% of all food items had at least three of the four types of SRIAs examined, with texture-related additives being the most common. Among sweets, 20% had all four types of SRIAs. <>Discussion: This work confirms the high prevalence of SRIAs in US packaged foods. They are ubiquitous in sweets, beverages, and RTE foods, but also present in substantial proportions of other food groups. Quantifying the presence of SRIAs in ingredient lists offers a novel way to identify UPFs for research; to distinguish more vs. less ultra-processed foods; and to test whether UPFs increase [the] risk for obesity-related conditions through additives that enhance the product's sensory qualities."[417.5]

[F] On Synthetic Food Dyes.

- *Red 40* (Allura Red AC) has been shown to cause DNA damage, & colon inflammation[1],
- *Yellow No. 6* (Sunset Yellow FCF) reduces the volume of different parts of the brain and results in anxiogenic effects[2],
- A mixture of Synthetic Food Dyes causes hyperactivity in young rats[3],
- Interestingly, *Blue No. 1* (Brilliant Blue FCF) has been shown to inhibit a protein called Pannexin-1 (Panx1), which associates with the initiation of inflammation in multiple tissue types[4]. Delving further into research on Pannexin-1, we find that its activity is necessary for myogenesis[4A], but that it is associated with aging-induced endothelial progenitor cell senescence which can be reversed by Panx1 downregulation[4B]. Furthermore, Panx1 appears to play a role in Amyloid-induced LTP suppression[4C].
- *Green No. 3* (Fast Green FCF) inhibits synaptic activity through decreased synaptic frequency, thereby facilitating LTD[4D].
- *Yellow No. 5* (Tartrazine) appears to promote the development, or at the very least, exacerbate the development of breast cancer.[4E]
- Many over-the-counter medications and vitamins, especially those geared towards children, contain synthetic food dyes.[4F]

[1] "<>The incidence of colorectal cancer (CRC) among young people has been on the rise for the past four decades and its underlying causes are only just starting to be uncovered. Recent studies suggest that consuming ultra-processed foods and pro-inflammatory diets may be contributing factors. The increase in the use of synthetic food colors in such foods over the past 40 years, including the common synthetic food dye Allura Red AC (Red 40), coincides with the rise of early-onset colorectal cancer (EOCRC).
<>As these ultra-processed foods are particularly appealing to children, there is a growing concern about the impact of synthetic food dyes on the development of CRC. Our study aimed to investigate the effects of Red 40 on DNA damage, the microbiome, and colonic inflammation. Despite a lack of prior research, high levels of human exposure to pro-inflammatory foods containing Red 40 highlight the urgency of exploring this issue. Our results show that Red 40 damages DNA both in vitro and in vivo and that consumption of Red 40 in the presence of a high-fat diet for 10 months leads to dysbiosis and low-grade colonic inflammation in mice. This evidence supports the hypothesis that Red 40 is a dangerous compound that dysregulates key players involved in the development of EOCRC."[417.7]

[2] "<>Sunset Yellow FCF (E110) is a water-soluble synthetic dye that has adverse neurobehavioral effects. Coenzyme Q10 (CoQ10) is known as a neuroprotective agent. The present study aimed to evaluate the effects of post-weaning exposure to Sunset Yellow FCF on behavioral and structural changes in the adult rat medial prefrontal cortex (mPFC) and the protective effects of CoQ10.
<>The weanling rats were randomly divided into six groups: distilled water, CoQ10 (10 mg/kg/day), and low (2.5 mg/kg/day) and high (70 mg/kg/day) doses of Sunset Yellow FCF with or without CoQ10 consumption for 6 weeks. A battery of behavioral tests including open field and Morris water maze tests were done at the end of the sixth week, and then the animals' brains were removed for stereological methods.
<>Our finding indicated that the high dose of Sunset Yellow FCF led to a reduced total volume of mPFC (15.16%), especially in the anterior cingulate cortex (ACC) region (21.96%), along with loss of neurons (32%) and glial cells (37%), which was associated with higher anxiety behavior and loss of spatial memory. However, CoQ10 prevented the neural loss and glial cells, improved anxiety-like behaviors, and memory impairment. On the other hand, the acceptable daily dose (low dose of Sunset Yellow FCF) did not show a discernible effect on the same parameters. This study showed that the CoQ10 can protect the alteration in mPFC structure and behavioral changes of the rats exposed to high dose of Sunset Yellow FCF."[417.8]

[3] "<>The consumption of artificial food dye (AFD) during childhood and adolescence has been linked to behavioural changes, such as hyperactivity. It is possible that the vulnerability to AFDs is modified by prenatal stress. Common consequences of prenatal stress include hyperactivity, thus potentially leading to synergistic actions with AFDs.
<>Here, we investigated the compounding effect of multigenerational prenatal stress (MPS) and AFD consumption on the development of hyperactivity and anxiety-related

behaviours across the lifespan in male rats. MPS treatment involved a family history of four consecutive generations of prenatal stress (F4 generation). AFD treatment included a 4%-concentration of FD&C Red 40, FD&C Yellow 5, FD&C Yellow 6, and FD&C Blue 1 in the drinking water from postnatal days 22 to 50 to resemble juvenile and adolescent dietary exposure. Using several exploration tasks, animals were tested in motor activity and anxiety-like behaviours from adolescence to 13 months of age.
<>MPS resulted in hyperactivity both early (50 days) and later in life (13 months), with normalized activity patterns at reproductive age. AFD consumption resulted in hyperactivity during consumption, which subsided following termination of treatment.
<>Notably, both MPS and AFD promoted risk-taking behaviour in young adults (3 months). There were few synergistic effects between MPS and AFD in this study. The findings suggest that AFDs exert the most noticeable effects at the time of exposure. MPS, however, results in a characteristic lifespan profile of behavioural changes, indicating that development and aging represent particularly vulnerable periods in life during which a family history of prenatal stress may precipitate."[417.9]

[4] "<>The food dye FD&C Blue No. 1 (Brilliant Blue FCF [BB FCF]) is structurally similar to the purinergic receptor antagonist Brilliant Blue G (BBG), which is a well-known inhibitor of the ionotropic P2X7 receptor (P2X7R). The P2X7R functionally interacts with the membrane channel protein pannexin 1 (Panx1) in inflammasome signaling. Intriguingly, ligands to the P2X7R, regardless of whether they are acting as agonists or antagonists at the receptor, inhibit Panx1 channels.
<>Thus, because both P2X7R and Panx1 are inhibited by BBG, the diagnostic value of the drug is limited. Here, we show that the food dye BB FCF is a selective inhibitor of Panx1 channels, with an IC50 of 0.27 μM. No significant effect was observed with concentrations as high as 100 μM of BB FCF on P2X7R. Differing by just one hydroxyl group from BB FCF, the food dye FD&C Green No. 3 exhibited similar selective inhibition of Panx1 channels. A reverse selectivity was observed for the P2X7R antagonist, oxidized ATP, which in contrast to other P2X7R antagonists had no significant inhibitory effect on Panx1 channels.
<>Based on its selective action, BB FCF can be added to the repertoire of drugs to study the physiology of Panx1 channels. Furthermore, because Panx1 channels appear to be involved directly or indirectly through P2X7Rs in several disorders, BB FCF and derivatives of this "safe" food dye should be given serious consideration for pharmacological intervention of conditions such as acute Crohn's disease, stroke, and injuries to the central nervous system." [417.10]

[4A] "<>Adult skeletal muscle has robust regenerative capabilities due to the presence of a resident stem cell population called satellite cells. Muscle injury leads to these normally quiescent cells becoming molecularly and metabolically activated and embarking on a program of proliferation, migration, differentiation, and fusion culminating in the repair of damaged tissue. These processes are highly coordinated by paracrine signaling events that drive cytoskeletal rearrangement and cell-cell communication.

<>Pannexins are a family of transmembrane channel proteins that mediate paracrine signaling by ATP release. It is known that Pannexin1 (Panx1) is expressed in skeletal muscle, however, the role of Panx1 during skeletal muscle development and regeneration remains poorly understood.
<>Here we show that Panx1 is expressed on the surface of myoblasts and its expression is rapidly increased upon induction of differentiation and that Panx1-/- mice exhibit impaired muscle regeneration after injury. Panx1-/- myoblasts activate the myogenic differentiation program normally, but display marked deficits in migration and fusion. Mechanistically, we show that Panx1 activates P2 class purinergic receptors, which in turn mediate a lipid signaling cascade in myoblasts. This signaling induces bleb-driven amoeboid movement that in turn supports myoblast migration and fusion. Finally, we show that Panx1 is involved in the regulation of cell-matrix interaction through the induction of ADAMTS (Disintegrin-like and Metalloprotease domain with Thrombospondin-type 5) proteins that help remodel the extracellular matrix. These studies reveal a novel role for lipid-based signaling pathways activated by Panx1 in the coordination of myoblast activities essential for skeletal muscle regeneration."[417.11]

[4B] "<>Background: We examined the role of Panxs (pannexins) in human endothelial progenitor cell (EPC) senescence.
<>Methods: Young and replication-induced senescent endothelial colony-forming cells (ECFCs) derived from human circulating EPCs were used to examine cellular activities and senescence-associated indicators after transfection of short interference RNA specific to Panx1 or lentivirus-mediated Panx1 overexpression. Hind limb ischemia mice were used as in vivo angiogenesis model. Protein and phospho-kinase arrays were used to determine underlying mechanisms.
<>Results: Panx1 was the predominant Panx isoform in human ECFCs and upregulated in both replication-induced senescent ECFCs and circulating EPCs from aged mice and humans. Cellular activities of the young ECFCs were enhanced by Panx1 downregulation but attenuated by its upregulation.
<>In addition, reduction of Panx1 in the senescent ECFCs could rejuvenate cellular activities with reduced senescence-associated indicators, including senescence-associated β-galactosidase activity, p16INK4a (cyclin-dependent kinase inhibitor 2A), p21 (cyclin-dependent kinase inhibitor 1), acetyl-p53 (tumor protein P53), and phospho-histone H2A.X (histone family member X).
<>In mouse ischemic hind limbs injected senescent ECFCs, blood perfusion ratio, salvaged limb outcome, and capillary density were all improved by Panx1 knockdown. IGF-1 (insulin-like growth factor 1) was significantly increased in the supernatant from senescent ECFCs after Panx1 knockdown. The enhanced activities and paracrine effects of Panx1 knockdown senescent ECFCs were completely inhibited by anti-IGF-1 antibodies. FAK (focal adhesion kinase), ERK (extracellular signal-regulated kinase), and STAT3 (signal transducer and activator of transcription 3) were activated in senescent ECFCs with Panx1 knockdown, in which the intracellular calcium level was reduced, and the activation was inhibited by supplemented calcium. The increased IGF-1 in Panx1-

knockdown ECFCs was abrogated, respectively, by inhibitors of FAK (PF562271), ERK (U0126), and STAT3 (NSC74859) and supplemented calcium.
<>Conclusions: Panx1 expression is upregulated in human ECFCs/EPCs with replication-induced senescence and during aging. Angiogenic potential of senescent ECFCs is improved by Panx1 reduction through increased IGF-1 production via activation of the FAK-ERK axis following calcium influx reduction. Our findings provide new strategies to evaluate EPC activities and rejuvenate senescent EPCs for therapeutic angiogenesis."[417.12]

[4C] "<>Beta-amyloid protein [Aβ(1-42)] plays an important role in the disease progress and pathophysiology of Alzheimer's disease (AD). Membrane properties and neuronal excitability are altered in the hippocampus of transgenic AD mouse models that overexpress amyloid precursor protein. Although gap junction hemichannels have been implicated in the early pathogenesis of AD, to what extent Pannexin channels contribute to Aβ(1-42)-mediated brain changes is not yet known.
<>In this study we, therefore, investigated the involvement of Pannexin1 (Panx1) channels in Aβ-mediated changes of neuronal membrane properties and long-term potentiation (LTP) in an animal model of AD. We conducted whole-cell patch-clamp recordings in CA1 pyramidal neurons 1 week after intracerebroventricular treatments of adult wildtype (wt) and Panx1 knockout (Panx1-ko) mice with either oligomeric Aβ(1-42), or control peptide.
<>Panx1-ko hippocampi treated with control peptide exhibited increased neuronal excitability compared to wt. In addition, action potential (AP) firing frequency was higher in control Panx1-ko slices compared to wt. Aβ-treatment reduced AP firing frequency in both cohorts. But in Aβ-treated wt mice, spike frequency adaptation was significantly enhanced, when compared to control wt and to Aβ-treated Panx1-ko mice. Assessment of hippocampal LTP revealed deficits in Aβ-treated wt compared to control wt. By contrast, Panx1-ko exhibited LTP that was equivalent to LTP in control ko hippocampi.
<>Taken together, our data show that in the absence of Pannexin1, hippocampi are more resistant to the debilitating effects of oligomeric Aβ. Both Aβ-mediated impairments in spike frequency adaptation and in LTP that occur in wt animals, are ameliorated in Panx1-ko mice. These results suggest that Panx1 contributes to early changes in hippocampal neuronal and synaptic function that are triggered by oligomeric Aβ."[417.13]

[4D] "The effects of the certified food dye Fast Green FCF (Food Green 3) on miniature synaptic events in whole-cell voltage clamped hippocampal interneurons were examined. Fast Green FCF reduced the frequency, but did not affect the amplitude or kinetics, of miniature synaptic events in a dose-dependent manner. At 1 mg/ml (1.2 mM), the frequency was reduced to 21% of control. The half-maximum effective concentration was estimated to be 200 microg/ml (250 microM). In contrast, the dye Phenol Red neither affected frequency, amplitude nor kinetics of synaptic events. The results suggest that

Fast Green FCF acts at a presynaptic locus, thereby inhibiting the release of neurotransmitter."[417.14]

[4E] "<>Background: Despite the considerable advances made in the treatment of cancer, it remains a global threat. Tartrazine (E102) is a synthetic dye widely used in food industries; it has recently been shown to induce oxidative stress (a well known risk factor of cancer) in rat tissues. The present work therefore aimed to assess the impact of a regular consumption of tartrazine on the incidence of breast cancer in rats.
<>Methods: Forty (40) Wistar rats aged 55 to 60 days were randomly assigned into 5 groups (n = 8) including two groups serving as normal controls and receiving distilled water (NOR) or tartrazine (NOR + TARZ). The three remaining groups were exposed to the carcinogen DMBA (50 mg/kg) and treated for 20 weeks with either distilled water (DMBA), tartrazine 50 mg/kg (DMBA + TARZ) or a natural dye (DMBA + COL). The parameters evaluated were the incidence, morphology and some biomarkers (CA 15–3, estradiol and α-fetoprotein) of breast cancer. The oxidative status and histomorphology of the tumors were also assessed.
<>Result: A regular intake of tartrazine led to an early incidence of tumors (100% in rats that received TARZ only vs 80% in rats that received DMBA only), with significantly larger tumors ($p < 0.001$) (mass = 3500 mg/kg and volume = 4 cm3). The invasive breast carcinoma observed on the histological sections of the animals of the DMBA + TARZ group was more developed than those of the DMBA group. The increase in serum α-fetoprotein ($p < 0.05$) and CA 15–3 ($p < 0.01$) levels corroborate the changes observed in tumors. The presence of oxidative activity in animals of the DMBA + TARZ group was confirmed by a significant decrease ($p < 0.001$) in the activity of antioxidant enzymes (SOD and catalase) as well as the level of GSH and increase in the level of MDA compared to the rats of the DMBA and NOR groups.
<>Conclusion: Tartrazine therefore appears to be a promoter of DMBA-induced breast tumorigenesis in rats through its oxidative potential. This work encourages further studies on the mechanisms of action of tartrazine (E102) and its limits of use."[417.15]

[4F] "<>Background: Food and Drug Administration (FDA) Food Drug and Cosmetic (FD&C) synthetic color additives (SCAs) have been associated with attentional and behavioral problems in children. Efforts to quantify exposure have focused on foods, while the contribution of medications and supplements remains unknown.
<>Objective: To estimate exposures to SCAs in children (2–16 years) and pregnant women from intake of common over-the-counter (OTC) medications and vitamins.
<>Methods: We estimated single-day exposure (mg/kg/day) to FD&C SCAs based on measurements of 25 different products and recommended dosages on product labels. Exposures were compared to SCA exposure estimates from food we previously developed and acceptable daily intakes (ADIs) established by FDA and the World Health Organization.
<>Results: The highest exposure was found for FD&C Red No. 40 in a children's cold/cough/allergy syrup. A child aged 12–16 years consuming the maximum daily

dosage would have an exposure of 0.221 mg/kg/day, which is twice this age group's typical exposure to this additive from food. No estimated exposures exceeded the ADIs. <>Significance: Some children's OTC medications and vitamins may cause daily SCA exposures comparable to those from foods. OTC medications and vitamins should be considered in efforts to quantify population exposure to FD&C SCAs."[417.16]

[G] A few intriguing parts of a research article on color and its influence on advertising written by Charles Spence:

"<>Sometimes, food products are given distinctive colors in order to help capture the consumer's visual attention for the importance of color to attentional capture by energy-dense food stimuli). This was presumably the case with the striking blue drink "Bolt from the blue" introduced by Innocent Smoothies. The growing popularity of blue wines and spirits also plays in this space of attention-capturing use of food color, as does recent launch of a bright blue mint chocolate dipping sauce for chicken by KFC in South Korea. A similar approach was successfully used almost two decades earlier when Heinz briefly launched green, purple, and blue variants of their tomato ketchup in the marketplace. Heinz reintroduced a green ketchup in a Shrek-themed marketing intervention. Burger King Japan used color to capture the attention of consumers by coloring its burgers and buns red and, on another occasion, black. Coco Pops switched temporarily from chocolate brown to white with the launch of their White Choc Coco Pops. Such strikingly unusual uses of food coloring have often proved successful in the marketplace.
<>So, for instance, Heinz temporarily captured an additional 10% market share in what has traditionally been a very slow-moving market simply by radically altering the colour of their ketchup. Notice how, in such cases, the attention-capturing use of color has no real "meaning" in terms of signaling the likely flavor of the product (which, to all intents and purposes, has not changed). While it has perhaps always been true that plants and animals have used color cues to attract or repel, in the contemporary era, it becomes difficult to know quite what particular role color cues may be playing in any given situation, especially when food colors are chosen primarily to capture attention."
"<>There is undoubtedly a trend-related element to the particular food colors that tend to be in and out of fashion. Here, one might consider only the phenomenal recent growth in popularity of rosé wines. Many commentators have been tempted to put this down to the drink's instagrammability.
<>Similarly, as has been mentioned already, coloring foods blue has also become very popular among the images that one finds displayed on Instagram. In part, this trend has been facilitated by the emergence of a number of natural blue food colorings. That said, few chefs have chosen to color any of their dishes blue, presumably because there is no justification for doing so from a flavor perspective."
"<>Technical developments mean that it is now possible to alter the visual appearance of food and drink using digital technologies, such as virtual reality (VR) and augmented reality (AR). In recent years, a number of sensory science researchers have investigated the consumers' response to food and drink whose visual appearance has been rendered in VR or AR. As such, it may not be too long before such color-changing technologies

make their way onto the menu at some top modernist restaurant or other. From there, it may only be a short jump to branded sensory apps that allow the consumer to modify the visual appearance of food at home. After all, there is already a growing interest among consumers in modifying the visual appearance of the foods they choose to post online. Color, be it the actual color of a food product, or virtual, will, then, likely continue to play a key role in the consumer's experience of food in the years ahead."[417.17] (Truncated for readability).

[See: The Brain: D2-Receptors]

Lipolytic Supplementation

Water: N/A POP

Water contributes to the process of lipolysis as H2O molecules are used to break down (hydrolyze) triglycerides for metabolic processing. It is possible that whereas optimal hydration facilitates lipolysis, dehydration facilitates glycogenolysis (glycogen breakdown), and if glycogen is exhausted—if glucose is not replaced through diet, proteolysis will take its place.

I must say I find it humorous how many fitness personalities suggest that those who exercise with a gallon jug of water are "stupid", when they are in fact ignorant of the supreme necessity of H2O for lipolysis.

[A] Water is the essential fat burner 1.

"<>Context: Drinking lots of water is commonly suggested as a part of weight loss regimens. However, only few systematic studies have addressed this notion. In this study, the effect of drinking 1500 ml of water, over and above the daily water intake on body weight, body mass index (BMI) and body composition of overweight subjects was assessed. Aim: To evaluate the role of drinking excessive water in weight reduction and body fat reduction of overweight subjects. Settings and Design: This study was conducted on 50 overweight girls for eight weeks, during which they were instructed to drink 500 ml of water, three times a day, half an hour before breakfast, lunch and dinner, which was over and above their daily water intake. <>Material and Methods: Body weight was measured in kilograms (kgs). BMI was calculated as weight in kilograms, which was divided by the square of height in metres. Body composition score was calculated as a sum of skin fold thickness in millimetres at three different sites, which was measured by using skin fold calipers. Pre and post-study body weight, body mass index and body composition scores were measured.
<>Results: The mean values of the pre-study and post-study body weight, body mass index and body composition scores were 65.86 kg and 64.42 kg, 26.7002 and 26.1224 and 79.626 mm and 76.578 mm respectively. All the three results were highly significant statistically.

<>Conclusions: The decrease in body weight, body mass index and body composition scores of overweight subjects at the end of study period establishes the role of water induced thermogenesis in weight reduction of overweight subjects."[418]

[A2] Water is the essential fat burner 2: Through Exercise-induced GH release.

"<>Design: Growth hormone (GH) has demonstrated water-retaining effects in subjects at rest, whereas other research has indicated that GH may stimulate sweating. Thus, the aim of this study was to investigate the effect of fluid intake on the exercise-induced GH response.
<>Methods: Seven healthy male volunteers (age: 27.4+/-1.3 years, weight: 74.5+/-1.1 kg, height: 179.3+/-2.3 cm) performed a 40-min submaximal rectangular cycling exercise in two different sessions. The first session (Session 1) was performed without water intake, and the second (Session 2) involved the ingestion of spring water (four intakes) corresponding to the volume of water lost during the first session. <>Results: In session 1, the water loss was 568+/-32 ml. In Session 2, the volume of water loss was not significantly different from the volume of fluid intake (524+/-16 versus 568+/-32 ml respectively). The decrease in plasma volume was significantly reduced in Session 2 (-6.69+/-1.59% versus -11.3+/-1.89%; P<0.05). In Session 1, the GH concentration was significantly lower than that during Session 2 after 25 min (3.04+/-1.05 versus 5.26+/-1.81; P<0.05) and after 40 min (13.7+/-3.55 versus 17.60+/-4.14 ng/ml; P<0.05) of exercise. The total GH response was significantly lower in Session 1 than in Session 2 (136.6+/-39.2 versus 202.4+/-58.9 ng/ml x min; P<0.05).
<>Conclusions: We conclude that the exercise-induced GH response decreases when exercise is performed without fluid intake."[419]

Agmatine: Low POP

Agmatine is an intriguing breakdown product of arginine metabolism that has neuroprotective effects, and although it inhibits iNOS[419.1], it enhances eNOS, and appears to promote angiogenesis in the brain after insult[419.2], but can have slightly suppressive effects on angiogenesis in higher concentrations on healthy tissue[419.3], and exerts anti-inflammatory effects on the body by promoting an M2 Macrophage pattern[419.4], therefore I consider it a better nootropic-lipolytic compound than Pro-Inflammatory compound, but that doesn't mean it shouldn't be incorporated into each cycle.

[A] Agmatine enhances cAMP, PGC1a, and PPARy thereby accelerating lipolysis and preventing high fat diet-induced weight gain.

"<>Agmatine (AGM), a product of arginine decarboxylation, influences multiple physiologic and metabolic functions. However, the mechanism(s) of action, the impact on whole body gene expression and metabolic pathways, and the potential benefits and risks of long term AGM consumption are still a mystery. Here, we scrutinized the impact of

AGM on whole body metabolic profiling and gene expression and assessed a plausible mechanism(s) of AGM action. Studies were performed in rats fed a high fat diet or standard chow. AGM was added to drinking water for 4 or 8 weeks. We used ^{13}C or ^{15}N tracers to assess metabolic reactions and fluxes and real time quantitative PCR to determine gene expression.
<>The results demonstrate that AGM elevated the synthesis and tissue level of cAMP. Subsequently, AGM had a widespread impact on gene expression and metabolic profiling including (*a*) activation of peroxisomal proliferator-activated receptor-α and its coactivator, PGC1α, and (*b*) increased expression of peroxisomal proliferator-activated receptor-γ and genes regulating thermogenesis, gluconeogenesis, and carnitine biosynthesis and transport. The changes in gene expression were coupled with improved tissue and systemic levels of carnitine and short chain acylcarnitine, increased β-oxidation but diminished incomplete fatty acid oxidation, decreased fat but increased protein mass, and increased hepatic ureagenesis and gluconeogenesis but decreased glycolysis. These metabolic changes were coupled with reduced weight gain and a curtailment of the hormonal and metabolic derangements associated with high fat diet-induced obesity.
<>The findings suggest that AGM elevated the synthesis and levels of cAMP, thereby mimicking the effects of caloric restriction with respect to metabolic reprogramming."[419.5]

[B] Agmatine is capable of promoting dendrite arborization and increased dendrite length, the first of which is a process that leads to synaptogenesis, the second is associated with synaptic plasticity[B2]. This means that Agmatine is a novel nootropic.

"<>Agmatine is an endogenous neuromodulator that has been shown to have beneficial effects in the central nervous system, including antidepressant-like effects in animals.
<>In this study, we investigated the ability of agmatine (0.1mg/kg, p.o.) and the conventional antidepressant fluoxetine (10mg/kg, p.o.) to reverse the behavioral effects and morphological alterations in the hippocampus of mice exposed to chronic corticosterone (20mg/kg, p.o.) treatment for a period of 21days as a model of stress and depressive-like behaviors. Chronic corticosterone treatment increased the immobility time in the tail suspension test (TST), but did not cause anhedonic-like and anxiety-related behaviors, as assessed with the splash test and the open field test (OFT), respectively. Of note, the depressive-like behaviors induced by corticosterone were accompanied by a decrease in hippocampal cell proliferation, although no changes in hippocampal neuronal differentiation were observed.
<>Our findings provide evidence that, similarly to fluoxetine, agmatine was able to reverse the corticosterone-induced depressive-like behaviors in the TST as well as the deficits in hippocampal cell proliferation. Additionally, fluoxetine but not agmatine, increased hippocampal differentiation. Agmatine, similar to fluoxetine, was capable of increasing both dendritic arborization and length in the entire dentate hippocampus, an effect more evident in the ventral portion of the hippocampus, as assessed with the modified Sholl analysis.

<>Altogether, our results suggest that the increase in hippocampal proliferation induced by agmatine may contribute, at least in part, to the antidepressant-like response of this compound in this mouse model of stress induced by chronic exposure to corticosterone."[419.6]

[B2] "<>Neurogenesis in the hippocampus is characterized by the birth of thousands of cells that generate neurons throughout life. The fate of these adult newborn neurons depends on life experiences. In particular, spatial learning promotes the survival and death of new neurons. Whether learning influences the development of the dendritic tree of the surviving neurons (a key parameter for synaptic integration and signal processing) is unknown.
<>Here we show that learning accelerates the maturation of their dendritic trees and their integration into the hippocampal network. We demonstrate that these learning effects on dendritic arbors are homeostatically regulated, persist for several months, and are specific to neurons born during adulthood.
<>Finally, we show that this dendritic shaping depends on the cognitive demand and relies on the activation of NMDA receptors. In the search for the structural changes underlying long-term memory, these findings lead to the conclusion that shaping neo-networks is important in forming spatial memories."[419.7]

Gamma Aminobutyric Acid (GABA: Oral): Low POP

Considering GABA enhances splenic Treg cells, and is anti-inflammatory, I believe GABA should be supplemented on the Anti-Cycle with higher carbohydrate consumption, frequent exercise, and the use of blood glucose lowering antioxidants, as it is a dual GH-Insulinemic fat burner. GABA can be supplemented with exercise, or consumed all day in your Myogenic Drink.

[A] GABA magnifies GH release when combined with exercise.

"<>Oral administration of the amino acid/inhibitory neurotransmitter gamma aminobutyric acid (GABA) reportedly elevates resting serum growth hormone (GH) concentrations. Purpose: To test the hypothesis that GABA ingestion stimulates immunoreactive GH (irGH) and immunofunctional GH (ifGH) release at rest and that GABA augments the resistance exercise-induced irGH/ifGH responses.
<>Methods: Eleven resistance-trained men (18-30 yr) participated in this randomized, double-blind, placebo-controlled, crossover study. During each experimental bout, participants ingested either 3 g of GABA or sucrose placebo (P), followed either by resting or resistance exercise sessions. Fasting venous blood samples were acquired immediately before and at 15, 30, 45, 60, 75, and 90 min after GABA or P ingestion and were assayed for irGH and ifGH.
<>Results: At rest, GABA ingestion elevated both irGH and ifGH compared with placebo. Specifically, peak concentrations of both hormones were elevated by about 400%, and the area under the curve (AUC) was elevated by about 375% ($P < 0.05$).

Resistance exercise (EX-P) elevated time-point (15-60 min) irGH and ifGH concentrations compared with rest ($P < 0.05$). The combination of GABA and resistance exercise (EX-GABA) also elevated the peak, AUC, and the 15- to 60-min time-point irGH and ifGH responses compared with resting conditions ($P < 0.05$). Additionally, 200% greater irGH ($P < 0.01$) and 175% greater ifGH ($P < 0.05$) concentrations were observed in the EX-GABA than in the EX-P condition, 30 min after ingestion. GABA ingestion did not alter the irGH to ifGH ratio, and, under all conditions, ifGH represented approximately 50% of irGH.
<>Conclusions: Our data indicate that ingested GABA elevates resting and postexercise irGH and ifGH concentrations. The extent to which irGH/ifGH secretion contributes to skeletal muscle hypertrophy is unknown, although augmenting the postexercise irGH/ifGH response may improve resistance training-induced muscular adaptations."[420]

[B] GABA use (2+ Grams chronically administered for human equivalency) results in both improved physical growth, beta cell mass, and reduced fat mass, and the GH response from GABA appears to be associated with Ghrelin release, although sadly these physiological effects appear to be sex-specific (male mice only).

"<>Background/Objectives: The amino acid γ-aminobutyric acid (GABA) is the primary neurotransmitter in the central nervous system (CNS) and acts as an autocrine and/or paracrine signaling molecule in various types of non-neuronal cells. On the other hand, GABA is a nutrient found in a variety of foods and is marketed as a health supplement based on a growing number of studies reporting health benefits in humans and recuperations in animal models of diseases. The present study sought to examine whether supplementation of GABA to young mice regulates their growth as well as glucose and lipid metabolism during physiological adolescence. Methods: Mice were supplemented with GABA over a 16-week period with subsequent anthropometric, metabolic, and endocrine measurements.
<>Results: Results showed that 16-week oral supplementation of GABA increased food consumption and body length while attenuating weight gain in male mice but not females. In addition, GABA treatment lowered the index of body fat (Lee index) and increased the expression of lipolytic enzymes in adipose and liver tissues of male mice without affecting blood glucose levels. Remarkably, supplementation of GABA significantly increased the protein expression of growth hormone (GH) in the pituitary gland of both male and female mice. However, it only substantially increased GH levels in the sera of male mice but not females. Moreover, GABA significantly increased the expression of the GH secretagogue peptide ghrelin in the stomachs of male mice only.
<>Conclusions: Together these novel findings suggest that long-term GABA supplementation fundamentally influences the growth and lipid metabolism of males during adolescent development by stimulating ghrelin–GH production and secretion. The mechanisms of GABA-induced sex-dependent upregulations of ghrelin and GH, as well as lipid metabolism in adolescence, await further studies."[421]

L-Histidine (Histamine): Moderate POP

The medical community would have you believe that hypersensitivity is a bad thing, that mild allergies are intolerable medical conditions, and through this propaganda they dose children and adults with strong antihistamines that not only weaken cognition, but also suppress muscle growth, and lipolysis. It is better to live life with a runny nose than to live life intellectually zombified, physically weak, and morbidly obese.

[A] Histidine consumption enhances systemic Histamine production.

"<>Three-week-old male rats were fed for two weeks diets supplying inadequate, adequate, or excess amounts of histidine. After the 2-week feeding of the experimental diets, the rats were killed. Brain, gastrocnemius muscle, kidney and stomach were removed and analyzed for histamine and free-histidine as well as for the degradative enzyme, HMT, and the histamine-synthesizing enzyme HDC. The following results were obtained: As the levels of dietary histidine increased, tissue concentrations of free-histidine and of histamine increased in all the tissues analyzed. <>The increase of histamine was greatest in brain and stomach (5- and 4-fold, respectively), but less in kidney and muscle (2-fold). HDC activity was not detected in muscle, but doubled from the lowest to the highest histidine intake in brain and increased almost 6-fold between the lowest and the highest histidine levels in stomach. Kidney HDC decreased from the lowest to the two higher levels of dietary histidine. HMT activity increased nominally in brain and not significantly in kidney; none was detected in either muscle or stomach. Brain and kidney, tissues with considerable HMT activity, had almost no histamine. <>The increases in tissue histamine concentrations observed in the tissues analyzed generally reflected the changes and magnitudes of enzyme activities for HMT and HDC. The results in the rat differ in important ways from those previously observed in chickens as follows: Histamine concentrations as a function in dietary histidine decreased in the chick. Both HDC and HMT activities were present in chick muscle tissue. HDC activity in chick stomach decreased sharply as a function of dietary histidine."[426]

[B] Histamine is necessary for myogenic proliferation.

"<>Histidine decarboxylase (HDC) catalyses the formation of histamine from L-histidine. Histamine is a biogenic amine involved in many physiological and pathological processes, but its role in the regeneration of skeletal muscles has not been thoroughly clarified. Here, using a murine model of hindlimb ischaemia, we show that histamine deficiency in Hdc knockout (Hdc-/-) mice significantly reduces blood perfusion and impairs muscle regeneration. Using Hdc-EGFP transgenic mice, we demonstrate that HDC is expressed predominately in CD11b+ Gr-1+ myeloid cells but not in skeletal muscles and endothelial cells. Large amounts of HDC-expressing CD11b+ myeloid cells are rapidly recruited to injured and inflamed muscles. Hdc-/- enhances inflammatory responses and inhibits macrophage differentiation. Mechanically, we demonstrate that histamine deficiency decreases IGF-1 (insulin-like growth factor 1) levels and diminishes

myoblast proliferation via H3R/PI3K/AKT-dependent signalling. These results indicate a novel role for HDC-expressing CD11b+ myeloid cells and histamine in myoblast proliferation and skeletal muscle regeneration."[427]

[C] Histamine exerts its lipolytic effect neuronally.

"<>Background: Hypothalamic neuronal histamine has been shown to increase lipolysis in white adipose tissue. The present study aimed to clarify whether peripheral loading with L-histidine, a precursor of neuronal histamine, may affect lipid metabolism in adipose tissue.
<>Materials and methods: The in vivo microdialysis study was used to assess lipolysis in rat epididymal adipose tissue by measuring the release of glycerol in response to administration of L-histidine. In addition, electrophysiological measurements were performed to record changes in activity of sympathetic nerve innervating adipose tissue following histidine treatment.
<>Results: Sequential administration of isoproterenol, a beta-adrenoceptor agonist, through the microdialysis cannula at concentrations of 10(-)8 to 10(-6) M increased the glycerol concentration in the dialysate dose-dependently ($P < 0.05$). Intraperitoneal administration of L-histidine at a dosage of 0.35 mmol kg(-1) also increased the glycerol concentration compared to that of phosphate buffered saline ($P < 0.05$). Concomitantly, the administration of histidine increased the serum concentration of free fatty acid compared to control treatment ($P < 0.05$). The accelerating effects of histidine on lipolysis were mimicked by the infusion of 10(2) nmol rat(-1) L-histamine into the third cerebroventricle ($P < 0.05$). Electrophysiological measurement demonstrated that administration of histidine at a dosage of 0.35 mmol kg(-1) increased the activity of efferent sympathetic nerve, innervating adipose tissue more than the infusion of phosphate buffered saline ($P < 0.05$).
<>Conclusion: The present results indicate that histidine accelerates lipolysis in white adipose tissue through activation of the sympathetic nerve. The regulation of lipolysis may therefore involve histamine neurons in the brain, probably through the conversion of L-histidine to histamine in the hypothalamus."[428]

Conjugated Linoleic Acid: Moderate POP

Conjugated Linoleic Acid (CLA) supplementation will accelerate fat loss and may potentially accelerate early muscle regeneration through increasing skeletal muscle inflammation, depending on the isomer mixture. Although, because CLA isomers inhibit angiogenesis, CLA should not be combined with my Pro-Inflammation Protocol, or used during Occlusion Training, as it will be best incorporated into Strength / Power Resistance Training protocols, or protocols involving Endurance Training for the purposes of promoting maximal lipolysis.

All CLA sold in stores in supplement form is extracted from processed Safflower oil, and there is limited to no research on the isomer concentration of these CLA Supplements in

medical literature, although [C] vaguely suggests differently. Thus, to gain a better understanding of the issue, I contacted the leading manufacturer of CLA, BASF (Tonalin CLA), about the isomer concentrations in their product, and was provided analytical testing results, which are displayed on the following page:

BASF

We create chemistry

Nutrition & Health

Product Specification	*FINAL*	Effective from	Feb 3, 2020

Tonalin® FFA 80 **PRD-No. 30531864**

® = Registered trademark of BASF group ™ = Trademark of BASF group DAWF-2019-01405 **Revision 4**

NOT FOR REGULATORY PURPOSES

Test parameter	Requirement	Test method
Characters		
Appearance	clear, colorless to slightly yellow oil	AX-001001
Tests		
Fatty acid composition		
Fatty acid C16:0	≤ 4.0 % (area)	IA-001011
Fatty acid C18:0	≤ 4.0 % (area)	IA-002011
Fatty acid C18:1, C9	10 to 20 % (area)	IA-003011
Fatty acid C18:2, C9, C 12	≤ 3.0 % (area)	IA-004011
Fatty acid C18:2 conjug.	78 to 84 % (area)	IA-005011
Fatty acid C18:2 C9, T11(1)	37.5 to 42.0 % (area)	IA-006011
Fatty acid C18:2 T10, C12(1)	37.5 to 42.0 % (area)	IA-007011
Fatty acid C18:2 conjug., TT isomers	≤ 1.0 % (area)	IA-009011

[HPLC graciously provided by Juergen Gierke at BASF]

The primary issue with CLA is that I am not certain of the dosing that should be used for weight loss, but I am reasonably confident that considering CLA accumulates in adipose tissue, even low doses are capable of causing subtle increases in fat loss. Unfortunately, in chronic use scenarios, the rapid fat loss CLA causes is not necessarily healthy due to insulin resistance, and liver damage, which is why when considering chronic CLA use,

one should only maintain this use for short periods of time or such as during emergency scenarios, while on very low carbohydrate and low fat diets (to avoid glucotoxicity and hyperlipidemia, as with less adipocytes comes less macronutrient storage capability). To mitigate the possible inflammatory damage caused by *chronic* dosages of CLA, certain antioxidant nutrients such as Alpha-Linolenic Acid, Docosahexaenoic Acid, and even Cineole may be enough to protect the body. If used in low dosages (a few grams per day), CLA will more than likely not result in any metabolic or physiological stress.

Certain isomers of CLA may cause muscle fiber changes, or other as-of-yet-unresearched biological effects, you should be prepared to experience changes to muscle strength or power when you consume chronic amounts of CLA. It could be anabolic for all that I know (towards Early Hypertrophy), and stimulate the growth of slow twitch fibers, but only time and careful analysis will tell.

[A] Conjugated Linoleic Acid isomers activate NF-kB in muscle tissue, and the isomer 10,12 CLA suppresses the essential muscle protein required for muscle contraction, Myosin Heavy Chain, possibly causing muscle type transformations (fast to slow).

"<>Scope: The capacity of skeletal muscle to contribute to glucose homeostasis depends on muscular insulin sensitivity. The expression of glucose transporter (GLUT)-4 is increased during myoblast differentiation, a process essential in maintenance of adult muscle. Therefore, processes that affect muscle differentiation may influence insulin dependent glucose homeostasis.
<>Conjugated linoleic acids, and in particular trans-10, cis-12 CLA (t10, c12-CLA), are potent inducers of NF-kB in cultured skeletal myotubes, and NF-kB activation inhibits muscle differentiation. The aims of this study were to evaluate whether CLAs inhibit myogenic differentiation and lower GLUT4 mRNA expression and to address the involvement of NF-kB activation in potential effects of CLA on these processes.
<>Methods and results: Incubation of C2C12 cells with t10, c12-CLA blocked the formation of myotubes, which was accompanied by reduced expression of the muscle specific genes creatine kinase, myogenin, myosin heavy chain perinatal and myosin heavy chain IIB, as well as decreased GLUT4 mRNA levels. However, genetic blockade of NF-kB was not sufficient to restore reduced myosin heavy chain protein expression following t10, c12-CLA treatment. Surprisingly, in contrast to myotubes, t10, c12-CLA was not able to activate NF-kB transcriptional activity in myoblasts."[429]

[B] CLA isomers are potent (brain) angiogenesis inhibitors.

"<>Conjugated Linoleic Acid (CLA) is fatty acid found endogenously in food sources that prevents new tumor development and reduces the growth of existing tumors in laboratory animals. CLA exerts its anti-carcinogenic effect by reducing VEGF and bFGF serum levels and by blocking flk-1 receptors, thereby inhibiting vascular growth critical to tumor growth and survival. Although the ability of CLA to inhibit angiogenesis in the peripheral nervous system is well characterized, it remains unknown whether CLA also affects vascular morphology in the central nervous system.

<>Therefore, in the present study, exercising and sedentary animals received either standard rat chow or a specially formulated diet consisting of 0.5% CLA for 24 days. The brains were then examined to determine the extent of vascular growth in the cerebellum, a region known to exhibit robust exercise-induced angiogenesis. Our results indicate that CLA administration significantly reduces angiogenesis in the cerebellum. This study is the first to demonstrate the anti-angiogenic effect of CLA in the brain and suggests that CLA be explored as a therapeutic treatment for cancer and tumors in the brain."[429.1]

[C] Only the 10,12 CLA isomer results in lipolysis after supplementation, at the cost of insulin resistance. This issue is expected, as the blood is flooded with free fatty acids, leading to a high level of Substrate Competition, and can therefore be mitigated through Ketogenic or low carb dieting during use, alongside the restriction in fatty acids to avoid hyperlipidemia. Furthermore, if high volume exercise is performed at a high frequency, this predicted CLA-induced hyperinsulinemia caused by adipose tissue insulin resistance and lipolysis is not as liable to cause as many complications, but if high volume exercise (Ideally Endurance Training) and diet are not carefully controlled, the body may experience metabolic stress.

"<>Conjugated linoleic acids (CLA) are a class of positional, geometric, conjugated dienoic isomers of linoleic acid (LA). Dietary CLA supplementation results in a dramatic decrease in body fat mass in mice, but also causes considerable liver steatosis. However, little is known of the molecular mechanisms leading to hepatomegaly. Although c9,t11- and t10,c12-CLA isomers are found in similar proportions in commercial preparations, the respective roles of these two molecules in liver enlargement has not been studied. <>We show here that mice fed a diet enriched in t10,c12-CLA (0.4% w/w) for 4 weeks developed lipoatrophy, hyperinsulinemia, and fatty liver, whereas diets enriched in c9,t11-CLA and LA had no significant effect. In the liver, dietary t10,c12-CLA triggered the ectopic production of peroxisome proliferator-activated receptor γ (PPARγ), adipocyte lipid-binding protein and fatty acid transporter mRNAs and induced expression of the sterol responsive element-binding protein-1a and fatty acid synthase genes. In vitro transactivation assays demonstrated that t10,c12- and c9,t11-CLA were equally efficient at activating PPARα, β/δ, and γ and inhibiting liver-X-receptor.
<>Thus, the specific effect of t10,c12-CLA is unlikely to result from direct interaction with these nuclear receptors. Instead, t10,c12-CLA-induced hyperinsulinemia may trigger liver steatosis, by inducing both fatty acid uptake and lipogenesis."[429.2]

[D] Another study displaying the lipolytic effects of CLA isomer 10,12 through two distinct mechanisms: adipocyte apoptosis (cellular suicide), and adipocyte shrinkage.

"<>Dietary conjugated linoleic acid (CLA) is a cancer chemopreventive agent that has been shown to inhibit angiogenesis in vivo and in vitro, and to decrease vascular endothelial growth factor (VEGF) and Flk-1 concentrations in the mouse mammary gland. To determine which isomer mediates the antiangiogenic effects of CLA in vivo, the effects of diets supplemented with 5 or 10 g/kg c9,t11- or t10,c12-CLA isomers were

compared in CD2F1Cr mice. Both isomers inhibited functional vascularization of a matrigel pellet in vivo and decreased serum VEGF concentrations; the t10,c12 isomer also decreased the proangiogenic hormone leptin ($P < 0.05$).
<>Additionally, the t10,c12 isomer, but not c9,t11-CLA, rapidly induced apoptosis of the white and brown adipocytes as well as the preexisting supporting vasculature of the mammary fat pad ($P < 0.05$). Independent of this isomer-specific adipose apoptotic effect, both isomers induced a rapid and reversible decrease in the diameter of the unilocular adipocytes ($P < 0.05$). The ability of both CLA isomers to inhibit angiogenesis in vivo may contribute to their ability to inhibit carcinogenesis. Moreover, we propose that each CLA isomer uniquely modifies the mammary stromal "soil" in a manner that is useful for chemoprevention of breast cancer."[429.3]

[E] CLA reduces endocannabinoid activity in the cerebellum, thereby potentially promoting cognitive processes (in younger individuals) and reducing food intake.

"<>Conjugated linoleic acid (CLA) has a role of biogenic regulation through modifying prostaglandin production. However, its effects on related metabolites of arachidonate remain unclear. Therefore, the effects of CLA on brain endocannabinoid content as well as its analogs were investigated. Mice (3-week-old), provided with diets containing 3% linoleic acid or 3% CLA for 4 weeks, were sacrificed and lipids were extracted from their cerebral cortex and hypothalamus. The amounts of N-arachidonoyl-ethanolamide, 2-arachidonoyl-glycerol (2-AG), oleoyl-ethanolamide and palmitoyl-ethanolamide were determined quantitatively by LC-MS. The 2-AG level in the cerebral cortex was significantly decreased by CLA treatment, but the other compounds were unaffected in the cerebral cortex and hypothalamus. The present study indicated that dietary CLA site-selectively decreases 2-AG in the cerebral cortex."[429.4]

[F] DHA prevents liver damage from CLA use, making these two compounds an interesting future combinatory supplement to manufacture.

"<>Background: Concomitant supplementation with docosahexaenoic acid (22:6 n-3; DHA) prevented trans-10, cis-12-conjugated linoleic acid (CLA)-induced nonalcoholic fatty liver disease (NAFLD) and insulin resistance. The effective dose of DHA and mechanisms involved are poorly understood.
<>Methods: We examined the ability of DHA (0.5% and 1.5%) to prevent increases in NAFLD and homeostatic model assessment of insulin resistance (HOMA-IR) induced by CLA (0.5%) when fed concomitantly for 4 weeks to C57BL/6N female mice. We also examined changes in expression of hepatic genes involved in fatty acid synthesis and oxidation.
<>Results: CLA supplementation increased liver triglycerides (TG) and HOMA-IR by 221% and 547%, respectively, and decreased mass of different adipose depots by 65%-90% when compared to those in the control group. When fed concomitantly, DHA prevented CLA-induced increases in liver TG and circulating insulin with varying efficiency, but it did not prevent loss in adipose tissue mass. In the CLA+0.5% DHA

group, the liver TG did not differ from those in the control group, but circulating insulin and HOMA-IR were 285% and 264%, respectively. In the CLA+1.5% DHA group, liver TG were 54% lower than those in the control group, but circulating insulin concentration and HOMA-IR did not differ between these two groups. CLA increased the expression of hepatic genes involved in fatty acid synthesis and decreased the expression of genes involved in fatty acid oxidation, and 1.5% DHA prevented changes in the expression of hepatic genes caused by CLA."[429.5]

[G] CLA promotes bone formation, and this effect is to be plausibly magnified through traditional strength training

"<>The bone undergoes continuous remodeling of osteoblastic bone formation and osteoclastic bone resorption to maintain proper bone mass. It is also reported that bone marrow adiposity has a reciprocal role in osteoblasts due to their same origin from mesenchymal stem cells. In addition, one of the key mediators of adipogenesis, peroxisome-proliferator activated receptor-γ (PPARγ), plays a significant role in osteoblastogenesis in bone marrow mesenchymal stem cells.

<>One dietary component that is known to have significant impact on adiposity and bone mass is conjugated linoleic acid (CLA). However, the link between controlling adiposity to improving bone mass by CLA has not been studied intensively. Thus, the purpose of this study is to determine the role of CLA on bone marrow adiposity and bone formation using murine mesenchymal stem cells.

<>The results confirmed that the trans-10,cis-12 CLA, but not the cis-9,trans-11 CLA isomer, significantly inhibited adipogenesis and promoted osteoblastogenesis from mesenchymal stem cells. The inhibition of adipogenesis by the trans-10,cis-12 CLA was mediated by PPARγ; however, the trans-10,cis-12 CLA had a direct effect on osteoblastogenesis which was independent to PPARγ in this model. The trans-10,cis-12 CLA also had significant effects on osteoclastogenesis inhibitory factor, which suggests potential influence of CLA on osteoclastogenesis.

<>Overall, the results suggest that the trans-10,cis-12, but not the cis-9,trans-11 CLA isomer, has a positive impact on bone health by both PPARγ mediated and independent mechanisms in mesenchymal stem cells."[429.6]

Yohimbine: Low POP

[A] Yohimbine is lipolytic by way of Adrenergic-2 Receptor Antagonism, which stimulates Norepinephrine release. It must be used in a low-insulin scenarios.

"<>The natural alpha-2 antagonist yohimbine promotes sympathetic activity by central as well as peripheral mechanisms, and yet in moderate doses dose not usually raise heart rate, increase blood pressure, or induce anxiety (in contrast to sympathomimetic drugs such as ephedrine). Administered prior to exercise, it boosts lipolysis and serum FFA levels both during and following exercise; blockade of adipocyte alpha-2 adrenoreceptors makes at least a modest contribution to this pro-lipolytic activity. These considerations suggest that pre-exercise administration of yohimbine will lower the respiratory quotient

during and following exercise, thus promoting fat loss. Since yohimbine can potentiate postprandial insulin secretion, its bariatric benefits should be greatest if administered on a schedule that minimizes postprandial yohimbine activity. A possible synergism of yohimbine and caffeine should be explored. Pre-exercise yohimbine administration has the potential to down-regulate the lipoprotein lipase activity of visceral adipocytes, increase lipolysis in refractory gynoid fat depots, and improve the impaired lipolytic response to exercise in the elderly."[430]

[B] Yohimbine appears to magnify neurogenesis when paired with a neurotrophic chemical.

"<>Adult hippocampal progenitors in vitro express all the α2-adrenoceptor subtypes, and decreased neurosphere frequency and BrdU incorporation indicate direct effects of α2-adrenoceptor stimulation on progenitors. Furthermore, coadministration of the α2-adrenoceptor antagonist yohimbine with the antidepressant imipramine significantly accelerates effects on hippocampal progenitor proliferation, the morphological maturation of newborn neurons, and the increase in expression of brain derived neurotrophic factor and vascular endothelial growth factor implicated in the neurogenic and behavioral effects of antidepressants.
<>Finally, short-duration (7 d) yohimbine and imipramine treatment results in robust behavioral responses in the novelty suppressed feeding test, which normally requires 3 weeks of treatment with classical antidepressants. Our results demonstrate that α2-adrenoceptors, expressed by progenitor cells, decrease adult hippocampal neurogenesis, while their blockade speeds up antidepressant action, highlighting their importance as targets for faster acting antidepressants."[431]

Allyl-Isocyanate (Wasabi): Low POP

Ally-Isocyanate promotes lipolysis at the cost of potential gastrointestinal toxicity. Sushi with Low Sodium Soy Sauce and Wasabi is the very best cheat meal on the planet, as the Allyl-Isocyanate will shuttle the elevated blood glucose from white rice directly into the muscles, the soy sauce will replenish blood sodium levels, & the raw fish will nourish you with DHA / EPA, and amino acids. Another option for its consumption is to add it to smoothies, or Protein Shakes.

"<>Allyl-isothiocyanate (AITC) is an organosulfur phytochemical found in abundance in common cruciferous vegetables such as mustard, wasabi, and cabbage. Although AITC is metabolized primarily through the mercapturic acid pathway, its exact pharmacokinetics remains undefined and the biological function of AITC metabolites is still largely unknown. In this study, we evaluated the inhibitory effects of AITC metabolites on lipid accumulation in vitro and elucidated the pharmacokinetics and tissue distribution of AITC metabolites in rats. We found that AITC metabolites generally conjugate with glutathione (GSH) or N-acetylcysteine (NAC) and are distributed in most organs and tissues. Pharmacokinetic analysis showed a rapid uptake and complete metabolism of

AITC following oral administration to rats. Although AITC has been reported to exhibit anti-tumor activity in bladder cancer, the potential bioactivity of its metabolites has not been explored. <>We found that GSH-AITC and NAC-AITC effectively inhibit adipogenic differentiation of 3T3-L1 preadipocytes and suppress expression of PPAR-γ, C/EBPα, and FAS, which are up-regulated during adipogenesis. GSH-AITC and NAC-AITC also suppressed oleic acid-induced lipid accumulation and lipogenesis in hepatocytes. Our findings suggest that AITC is almost completely metabolized in the liver and rapidly excreted in urine through the mercapturic acid pathway following administration in rats. AITC metabolites may exert anti-obesity effects through suppression of adipogenesis or lipogenesis."[431.1]

Raspberry Ketone: Moderate POP

A relatively toxic chemical that may have benefits if used in moderate dosages.

[A] "<>Raspberry ketone (4-(4-hydroxyphenyl) butan-2-one; RK) is a major aromatic compound of red raspberry (Rubus idaeus). The structure of RK is similar to the structures of capsaicin and synephrine, compounds known to exert anti-obese actions and alter the lipid metabolism. The present study was performed to clarify whether RK helps prevent obesity and activate lipid metabolism in rodents. To test the effect on obesity, our group designed the following in vivo experiments: 1) mice were fed a high-fat diet including 0.5, 1, or 2% of RK for 10 weeks; 2) mice were given a high-fat diet for 6 weeks and subsequently fed the same high-fat diet containing 1% RK for the next 5 weeks.
<>RK prevented the high-fat-diet-induced elevations in body weight and the weights of the liver and visceral adipose tissues (epididymal, retroperitoneal, and mesenteric). RK also decreased these weights and hepatic triacylglycerol content after they had been increased by a high-fat diet. RK significantly increased norepinephrine-induced lipolysis associated with the translocation of hormone-sensitive lipase from the cytosol to lipid droplets in rat epididymal fat cells.
<>In conclusion, RK prevents and improves obesity and fatty liver. These effects appear to stem from the action of RK in altering the lipid metabolism, or more specifically, in increasing norepinephrine-induced lipolysis in white adipocytes."[431.2]

[A2] Raspberry Ketone elicits fat loss through appetite suppression, but in high dosages it is damaging to the thymus, an organ that is necessary for immune cell production, leading to systemic inflammation.

"<>Raspberry ketone (RK; [4-(4-hydroxyphenyl)-2-butanone]) is used by the food and cosmetic industry as a flavoring agent. RK is also marketed as a dietary supplement for weight maintenance and appetite control. The purpose of the study was to characterize the acute feeding suppression with RK (64-640 mg/kg) by oral gavage in male and female C57BL/6J mice. Cumulative 24 h food intake was reduced at 200 mg/kg (24%

feeding suppression) in males and reliably reduced at 640 mg/kg (49-77% feeding suppression).
<>Feeding suppression was not associated with pica behavior over the range of doses or conditioned taste aversion. In a separate experiment, a single oral gavage of RK (640 mg/kg) resulted in approximate 43% mortality rate (6 out 14 male mice) within 2 days.
<>Atrophy of white adipose tissue, splenic abnormalities, and thymus involution were noted after 2-4 days after oral gavage RK. Total white blood cell count, lymphocytes, monocytes, eosinophils were significantly lower, while mean red blood cells, hemoglobin, and hematocrit were significantly higher with RK treatment. Our findings indicated a dose-dependent feeding suppression with acute RK, but doses that reliable suppress food intake are associated with pathological changes."[431.3]

Piperine: High POP

Piperine would appear to be better utilized as fat burner rather than bioavailability enhancer [1], and this effect appears to be mediated by the MC-4 receptors, or more likely, AMPK expression [2].

[1] "<>Objective: The present study was undertaken to explore the effect of piperine in obesity-induced dyslipidemia.
<>Materials and Methods: Male Sprague Dawley rats were fed high-fat diet (HFD) for the first eight weeks, to develop obesity-induced dyslipidemia. Later on piperine (40 mg / kg) and sibutramine (5 mg / kg) were administered for three weeks along with the continuation of HFD to two separate groups, which served as the test and standard groups, respectively. Body weight, food intake, serum triglyceride, total cholesterol, LDL, VLDL, and HDL were measured at the end of the fourth, eighth (before treatment), and eleventh (after treatment) week, while the fat mass was measured at the end of the eleventh week in the normal, HFD-control, test, and standard groups.
<>Results: Supplementing piperine with HFD significantly reduced not only body weight, triglyceride, total cholesterol, LDL, VLDL, and fat mass, but also increased the HDL levels, with no change in food intake.
<>Conclusion: The above results suggest that piperine possesses potential fat reducing and lipid lowering effects, without any change in food appetite, at a small dose of 40 mg / kg. The mechanism of action for such an activity needs to be determined. However, looking to structural similarity with the presently known Melanocortin-4 (MC-4) agonists, involvement of MC-4 receptors in its activity can be guessed."[431.4]

[2] "<>This study characterizes the human metabolic response to piperine, a curcumin extract, and the details of its underlying molecular mechanism. Using 1H-NMR-based metabolome analysis, we showed the metabolic effect of piperine on skeletal muscle and found that piperine increased the level of intracellular lactate, an important metabolic intermediate that controls expression of several genes involved in mitochondrial activity.
<>Piperine also induced the phosphorylation of AMP-activated protein kinase (AMPK) and its downstream target, acetyl-CoA carboxylase (ACC), while additionally stimulating

glucose uptake in an AMPK dependent manner. Piperine also stimulates the p38 mitogen-activated protein kinase (p38 MAPK), an effect that was reversed by pretreatment with compound C, an AMPK inhibitor.
<>Inhibition of p38 MAPK resulted in no piperine-induced glucose uptake. Increased level of lactate resulted in increased expression of mitochondrial uncoupling protein 1 (UCP1), which regulates energy expenditure, thermogenesis, and fat browning. Knock-down of AMPK blocked piperine-induced UCP1 up-regulation, demonstrating the required role of AMPK in this effect. Taken together, these results suggest that piperine leads to benign metabolic effects by activating the AMPK-p38 MAPK signaling pathway and UCP1 expression by activating intracellular lactate production in skeletal muscle."[431.4.0]

Wakame (Undaria Pinnatifida): POP N/A

Wakame is a seaweed that contains large concentrations of the carotenoid antioxidant Fucoxanthin, which is similar to Astaxanthin. Fucoxanthin shows antiobesity effects through the activation of UCP1 in white adipose tissue. I would suggest only ordering it from Korean companies, for better quality control.

"<>Mitochondrial uncoupling protein 1 (UCP1) is usually expressed only in brown adipose tissue (BAT) and a key molecule for metabolic thermogenesis to avoid an excess of fat accumulation. However, there is little BAT in adult humans. Therefore, UCP1 expression in tissues other than BAT is expected to reduce abdominal fat. Here, we show reduction of abdominal white adipose tissue (WAT) weights in rats and mice by feeding lipids from edible seaweed, Undaria pinnatifida. Clear signals of UCP1 protein and mRNA were detected in WAT of mice fed the Undaria lipids, although there is little expression of UCP1 in WAT of mice fed control diet. The Undaria lipids mainly consisted of glycolipids and seaweed carotenoid, fucoxanthin. In the fucoxanthin-fed mice, WAT weight significantly decreased and UCP1 was clearly expressed in the WAT, while there was no difference in WAT weight and little expression of UCP1 in the glycolipids-fed mice. This result indicates that fucoxanthin upregulates the expression of UCP1 in WAT, which may contribute to reducing WAT weight."[431.4.1]

Phytohemagglutinin: POP N/A

An interesting chemical and a Lectin ("Antinutrient") found in fresh, dried, or cooked red kidney beans that has been shown to activate UCP1 and thereby promote energy expenditure. I am of course not suggesting consuming raw red kidney beans as this compound is quite toxic to skeletal muscle cells, but that does not discount its potential uses in very, very low concentrations, as even store bought canned Dark Red Kidney Beans still appear to contain small amount of Phytohemagglutinin.

"<>Despite all modern advances in medicine, there are few reports of effective and safe drugs to treat obesity. Our objective was to screen anti-obesity natural compounds, and to

verify whether they can reduce the body weight gain and investigate their molecular mechanisms. By using drug-screening methods, Phytohemagglutinin (PHA) was found to be the most anti-obesity candidate natural compound.
<>Six-week-old C57BL/6J mice were fed with a high-fat diet (HFD) and intraperitoneally injected with 0.25 mg/kg PHA everyday for 8 weeks. The body weight, glucose homeostasis, oxygen consumption and physical activity were assessed. We also measured the heat intensity, body temperature and the gene expression of key regulators of energy expenditure. Prevention study results showed PHA treatment not only reduced the body weight gain but also maintained glucose homeostasis in HFD-fed mice.
<>Further study indicated energy expenditure and uncoupling protein 1 (UCP1) expression of brown adipose tissue (BAT) and white adipose tissue (WAT) in HFD-fed mice were significantly improved by PHA. In the therapeutic study, a similar effect was observed. PHA inhibited lipid droplet formation and upregulated mitochondrial-related gene expression during adipogenesis in vitro. UCP1 KO mice displayed no differences in body weight, glucose homeostasis and core body temperature between PHA and control groups. Our results suggest that PHA prevent and treat obesity by increasing energy expenditure through upregulation of BAT thermogenesis."[431.5]

Coconut oil: Low POP

Coconut oil rather than MCT oil alone, promotes brown fat activity and mitochondrial biogenesis, resulting in lipolysis. Although it can be said that the overconsumption of Lauric acid when combined with carbohydrates will perturb metabolism, if consumed in moderation, during a low carb diet, while fasting, or during a Ketogenic Diet, where energy intake is decreased, it should pose little threat to lipolysis, but I must clarify that considering Lauric acid is such an energy dense lipid, excessive consumption of it may perturb lipolysis by a small degree, therefore it is safer during Emergency Lipolytic scenarios to use Coconut-oil based MCT oil.

"<>Coconut oil (CO) and its main ingredients, medium-chain fatty acids (MCFA), present many benefits. Whether MCFA and CO play an equally valuable role in anti-obesity remains unclear. This study compared the anti-obesity effects of CO and MCFA [octanoic acid (C8:0) and decanoic acid (C10:0)] to gain insight into the underlying mechanism.
<>Male C57BL/6J mice were fed either a low-fat diet (LFD) or high-fat diet (100% HFD) replaced with 2.5% MCFA (97.5% HFD + 2.5% MCFA) or 5% CO (95% HFD + 5% CO) for 17 weeks.
<>CO and MCFA ameliorated the HFD-induced abnormal body and adipose depot weights, insulin sensitivity, and energy expenditure (EE), which was associated with brown adipose tissue (BAT) thermogenesis.
<>Furthermore, CO enhanced the expression of thermogenesis markers in BAT, which was consistent with increased BAT activity. CO showed a better effect than MCFA in activating BAT to increase thermogenesis and energy metabolism to combat obesity, which may be attributed to the cooperation of MCFA and other substances in CO. This

work provides evidence for the anti-obesity effects of CO, which could be a better alternative to lard in daily diet, rather than pure MCFA."[431.6]

Brown Rice / Gamma-Oryzanol (y-Oryzanol): Low–High POP

Gamma-Oryzanol (a mixture of plant phytochemicals found in brown rice) appears to counteract the downregulated Dopamine-2 receptor function that develops as a result of a high fat diet, thereby reducing fat cravings[A]. Even a diet high in Brown Rice (low levels of y-Oryzanol) was shown to protect the brain from high fat diet-induced behavior derangements through reducing Endoplasmic Reticulum stress (simplified as cellular stress: neurotoxicity) in the brain and reversing the Leptin (satiety hormone) resistance[B]. I believe that the specially formulated high fat diet used in this study, and likely many other rodent studies, is the "Clinton/Cybulsky High Fat Rodent Diet"[431.9], which contains very high concentrations of non-essential adipogenic fatty acids, such as Palmitic acid, Oleic acid, and Stearic acid, owing to very large amounts of Cocoa Butter, with a smaller amount of Soybean oil, containing Linoleic acid and Oleic acid, in the ratio of 31:5. Therefore do not conflate, like *many* uninformed individuals (and researchers) do, the obesogenic effects of non-essential fats to essential fats. As to the question of arsenic content, I do not know.

[A] "<>Aims/hypothesis: Overeating dietary fats causes obesity in humans and rodents. Recent studies in humans and rodents have demonstrated that addiction to fats shares a common mechanism with addiction to alcohol, nicotine and narcotics in terms of a dysfunction of brain reward systems. It has been highlighted that a high-fat diet (HFD) attenuates dopamine D2 receptor (D2R) signalling in the striatum, a pivotal regulator of the brain reward system, resulting in hedonic overeating. We previously reported that the brown rice-specific bioactive constituent γ-oryzanol attenuated the preference for an HFD via hypothalamic control. We therefore explored the possibility that γ-oryzanol would modulate functioning of the brain reward system in mice.
<>Methods: Male C57BL/6J mice fed an HFD were orally treated with γ-oryzanol, and striatal levels of molecules involved in D2R signalling were evaluated. The impact of γ-oryzanol on DNA methylation of the D2R promoter and subsequent changes in preferences for dietary fat was examined. In addition, the effects of 5-aza-2'-deoxycytidine, a potent inhibitor of DNA methyltransferases (DNMTs), on food preference, D2R signalling and the levels of DNMTs in the striatum were investigated. The inhibitory effects of γ-oryzanol on the activity of DNMTs were enzymatically evaluated in vitro.
<>Results: In striatum from mice fed an HFD, the production of D2Rs was decreased via an increase in DNA methylation of the promoter region of the D2R. Oral administration of γ-oryzanol decreased the expression and activity of DNMTs, thereby restoring the level of D2Rs in the striatum. Pharmacological inhibition of DNMTs by 5-aza-2'-deoxycytidine also ameliorated the preference for dietary fat. Consistent with these findings, enzymatic in vitro assays demonstrated that γ-oryzanol inhibited the activity of DNMTs.

<>Conclusions/interpretation: We demonstrated that γ-oryzanol ameliorates HFD-induced DNA hypermethylation of the promoter region of D2R in the striatum of mice. Our experimental paradigm highlights γ-oryzanol as a promising antiobesity substance with the distinct property of being a novel epigenetic modulator."[431.7]

[B] BR = Brown Rice, WR = White Rice, HFD = High Fat Diet, Orz = y-Oryzanol, ER = Endoplasmic Reticulum (Stress).

"<>C57BL/6J mice were fed BR or WR for 10 weeks, and their body weight and food intake were monitored."
"<> To investigate the effect of BR on hypothalamic ER stress, we analyzed the mRNA levels of ER stress–responsive genes such as CCAAT/enhancer-binding protein-homologous protein (Chop), endoplasmic reticulum resident DNAJ 4 (ERdj4), and the spliced form of X-box binding protein 1 (Xbp1s). In response to ER stress, Xbp1 mRNA is spliced into its active form by inositol-requiring protein 1 (IRE1). The mRNAs of ER stress–responsive genes were highly expressed in the hypothalamus compared with the liver (Chop, 7.5-fold; ERdj4, 9.3-fold; Xbp1s, 1.6-fold. The mRNA levels of ER stress–responsive genes were significantly upregulated in the hypothalami of the mice fed the HFDs compared with those fed the CDs (Chop, 1.5-fold; ERdj4, 2.6-fold; Xbp1s, 1.5-fold. BR did not affect the mRNA levels of Chop, ERdj4, or Xbp1s in the hypothalami of the mice fed the CDs. However, BR significantly decreased the mRNA levels of Chop, ERdj4, and Xbp1s in the hypothalami of the mice fed the HFDs (42, 36, and 38% reduction vs. HFD + WR, respectively."
"<> Previous reports indicated that ER stress contributes, at least in part, to the development of leptin resistance through inflammatory pathways. Thus, the mRNA levels of inflammatory cytokines in the hypothalamus were investigated. The results showed a similar trend to ER stress–responsive genes. The plasma leptin levels of the mice fed the HFDs were significantly greater than those of the mice fed the CDs (13.8 ± 1.8 vs. 2.3 ± 0.7 ng/mL). BR significantly decreased plasma leptin levels in mice the HFD (7.1 ± 2.0 vs. 13.8 ± 1.8 ng/ mL). To assess hypothalamic leptin sensitivity, phosphorylation of STAT3 was measured. The intracerebroventricular administration of leptin substantially increased STAT3 phosphorylation in hypothalami from mice fed the CDs. The levels of STAT3 phosphorylation were significantly decreased in mice fed the HFDs (31 ± 0.1% vs. CD), indicating insensitivity to leptin. However in mice fed the HFDs, BR significantly increased leptin-induced STAT3 phosphorylation compared with WR (1.9-fold vs. HFD + WR), indicating that BR ameliorated hypothalamic leptin resistance."
"<>To investigate the effect of BR on feeding behavior, we measured food consumption for 8 weeks when mice were allowed to choose freely between the CDs and HFDs. Total food intake did not differ among control, WR, and BR groups (data not shown). The control group strongly preferred the HFD. In contrast, in the group fed the diet containing BR, the HFD preference was decreased significantly (∼15.0% reduction vs. control, ∼11.4% reduction vs. WR diet group), leading to decreased body weight gain (control, 32.94 ± 1.33 g; WR, 31.69 ± 0.92 g; BR, 30.28 ± 0.44 g)."

"<>Oral Orz administration did not affect the body weights or plasma insulin levels of the mice fed the HFDs (plasma insulin: control, 451 ± 88 pg/mL; Orz 20, 405 ± 61 pg/mL; Orz 80, 495 ± 115 pg/mL; Orz 320, 218 ± 27 pg/mL); however, Orz significantly decreased blood glucose levels of these mice (vehicle, 157 ± 8 mg/mL; Orz 20, 131 ± 5 mg/mL; Orz 80, 127 ± 4 mg/mL; Orz 320, 128 ± 5 mg/mL)."
"<>To investigate the effect of Orz on ER stress in primary neuronal cells, cells were pretreated with Orz (0.1, 1 μmol/L) for 2 h and then stimulated with tunicamycin (0.1 μg/mL). Pretreatement of cells with Orz (1 μmol/L) significantly suppressed the expression of ER stress–responsive genes (Chop, 83%; ERdj4, 81%; and Xbp1s, 90% of vehicle."[431.8][431.9]

Hypothermic Alcoholic Browning (HAB)

As it turns out, Alcohol increases brown fat formation through enhancing Retinoic Acid signaling in white adipose tissue, and it may be possible to magnify this effect by combing low-moderate dose alcohol consumption with Hypothermia Therapy, although there will be obvious risks, such as hypothermic death, which is why one should never experiment with my idea without the supervision of a friend or family member, and the obvious approval of a licensed doctor.

"<>Clinically, low and moderate alcohol intake improves human health with protection against metabolic syndromes, including type 2 diabetes; however, mechanisms that are associated with these effects remain to be elucidated. The aims of this study were to investigate the effects of moderate alcohol intake on thermogenic brown/beige adipocyte formation and glucose and lipid homeostasis, as well as the involvement of retinoic acid (RA) signaling in the entire process.
<>C57BL6 male mice were supplemented with 8% (w/v) alcohol in water for 1 or 4 mo. Alcohol intake prevented body weight gain, induced the formation of uncoupling protein 1–positive beige adipocytes in white adipose tissue, and increased thermogenesis in mice, which is associated with decreased serum glucose and triacylglycerol levels. Mechanistically, alcohol intake increased RA levels in serum and adipose tissue, which was associated with increased expression of aldehyde dehydrogenase family 1 subfamily A1 (Aldh1a1). When RA receptor-α signaling was conditionally blocked in platelet-derived growth factor receptor-α-positive adipose progenitors, the effects of alcohol on beige adipogenesis were largely abolished. Finally, moderate alcohol prevented high-fat diet-induced obesity and metabolic dysfunction.
<>In conclusion, moderate alcohol intake induces thermogenic brown/beige adipocyte formation and promotes glucose and lipid oxidation via elevation of RA signaling."[431.10]

[See: The Ketogenic Diet: [H] (L-Carnitine)]

[See: Anti-Inflammation Cycle Supplementation: Silymarin (AKT Suppressor)]

[See: Fructose, Sucrose, & Advanced Glycation End Products: AGE Inhibitors: Alpha Lipoic acid]

[See: Dietary Fatty Acids: Alpha-Linolenic Acid]

[See: Pro-Inflammation Cycle Supplementation: L-Glutamine]

[See: Anti-Inflammation Cycle Supplementation: Betaine]

[See: Short Chain Fatty Acids: Acetate-Vinegar]

The Ketogenic Diet

This diet works by decreasing the sugar in the bloodstream thereby enhancing IL-6 release in muscle, catecholamines release, and ketone production, which in turn facilitates muscle hypertrophy & lipolysis, but an extended ketogenic diet causes damage to the pancreas:

"<>After 22 wk, β-cell mass in KD-fed mice, determined by analyzing 175.1 ± 7.1 mm2 pancreatic tissue/mouse, was decreased. The density of islets was unchanged, but the median β-cell cluster size was significantly decreased"[433].

A cycle of 7-14 Days On Keto and 1-2 days Off Keto seems to be superb idea, commonly taught by older bodybuilders. Contrary to popular belief, *endogenously* produced ketones do not play a significant role in lipolysis, it is primarily the enhanced IL-6 activity in muscle tissue that burns fat, although endogenously produced ketones exert a systemic antioxidant effect through HDAC inhibition, the real benefits from ketones will be experienced from chronically administered exogenous ketones (BHB).

Do not be fooled by the online suggestions of "low carb keto", you will burn more fat and gain more muscle on a zero carbohydrate ketogenic diet (Zero-K Diet) with a low consumption of linoleic acid and lauric acid, and high consumption of MCT oil, consuming only lean meats, eggs, and low fat cheeses. If you instead choose to be fooled by health trends and try a "Low Carb Ketogenic Diet" / "Modified Ketogenic Diet" that includes fruit, you'll be substantially suppressing your ketogenic metabolism in multiple ways, see: Micro-Essays: Fasting, Detoxification, & "Fasting Diets": Pg. 951. Furthermore, the advent of "carb free" bread and snack products, made of wheat protein, do not seem particularly healthy to me, and even if they are, why confuse your body by consuming food with grainy, carbohydrate-like flavor? It is good to learn to control your cravings for carbohydrates (grains and sweets), it strengthens your resolve, and makes it all the more rewarding to return to dietary normalcy when you finally reach your weight loss goal.

When you consume your cheat meal(s), you should consume copious amounts of probiotic supplements, alongside fermented / probiotic foods such as Cottage Cheese,

Yogurt, Sauerkraut, & Kimchi to feed your microbiome. Although it may seem that you have *earned* the sensory pleasures of junk food on your cheat day(s), you should still stay away from Fructose and Palmitic acid-rich foods as they will only make you sickly, and remember that it is a dangerous animalistic regression to treat food as a drug.

Nicotine and Alcohol generally must be avoided for their interference with IL-6, and insulinemic properties, and if possible, you should schedule your high volume workout phases on a ketogenic diet cycle, as angiopotential should in theory be magnified. However, in terms of lipolysis, Nicotine can be used for short periods of time on a Ketogenic Diet to stimulate angiogenesis, and an alternative form of free fatty acid mobilization (AMPKa2 vs IL-6).

The "Keto Flu" is a symptom of either excessive inflammation (IL-6) in the body, Beta-cell death, or nutrient deficiencies, especially electrolytes such as Potassium, Sodium, and Magnesium.

It is an excellent idea to combine a Ketogenic Diet with Leucine Cycling, meaning you restrict fast digesting protein powder supplementation, which is often gluconeogenic, and insulinemic, and replace it with Leucine powder, see: Micro-Essays: Leucine Cycling, Fast / Slow Specializations, & The Protein Myth: Pg. 1074.

Although it may be easier to call this diet the "Carnivore Diet" or the "Atkins Diet" it is important to recognize and respect the historical and scientific origins from which this diet evolved. The ideas behind this diet are not new as they predate modern dietary trends and have roots in ancient medical practices. The significance and earliest neologism of "Ketosis" and Ketogenic Diet were made by the physicians *Garrod and Hopkins* who recognized a novel anticonvulsant process in the study and treatment of epilepsy, stemming from groundbreaking research on the benefits of fasting and the role of ketone bodies in the blood. The rebranding of the Ketogenic Diet disrespects and attempts to reattribute Garrod and Hopkins' intellectual work (vis-a-vi Robert Atkins) and overlooks the extensive history and scientific developments that took place to shape our understanding of this amazing dietary discovery.

One would assume that the body adapts rapidly to a low glucose state by increasing fatty acid oxidation, however this is only partially true, for even during strong periods of ketosis, the body may still have difficulty breaking down a large amount of long chain fatty acids, even Lauric acid found in Coconut oil, thus leading to Ceramide production, this is called "**Incomplete Beta-oxidation**" and is a common side effect of high fat diets. To avoid this, Endurance Training (60-Minutes Moderate Intensity Steady-state Cardio) or HIIT must be performed at a high frequency, and if these mitochondria-boosting workouts are not performed, it is a far better idea to replace vegetable and seed oils with Coconut-based MCT oil on your Ketogenic Diet, as these fatty acids are easily metabolized due to their short carbon chains (even if they show suppressive effects on angiogenesis), or you can rely on L-Carnitine [H]. If you consume large amounts of Lauric acid, Oleic acid, Palmitic acid, or Linoleic acid on a Ketogenic Diet while not stimulating mitochondria biogenesis & efficiency through Endurance Training, or HIIT (cardio), while only engaging in high load, low volume training, you will perturb your

metabolism and reduce lipolytic efficiency, leading to greater intramuscular lipid accumulation, and future sickness (depending on if you cycle between Keto diets and Carb diets), we can simplify high fat dieting as being ideally dependent on exercise volume, therefore to remain healthy on a Strength-only protocol (- ARCS) one should not consume an excessive amount of fatty acids, See: Myokines: PGC1a.

Note: Do not consume large amounts of caffeine on a Ketogenic Diet, it's anti-angiogenic effects will counteract one of the primary and most beneficial physiological effects of this diet, but if you do, ensure it is a caffeine source relatively devoid of antioxidants, such as Coffee, or Caffeine Pills, and it makes zero sense to suppress both angiogenesis and Interleukin-6 through polyphenol consumption while substantially restricting carbohydrates. If you find yourself unable to avoid the consumption of a morning eugeroic drug, it is a better option to cycle between one week of Caffeine use, and one week of Nicotine use, then to constantly consume caffeine, everyday single day, or even wiser would be utilize Sildenafil as a morning vasodilatory nootropic.

[A] The Ketogenic Diet substantially enhances IL-6 in slow twitch muscles which explains its lipolytic and myogenic effects.

"<>IL-6 mRNA increased dramatically by approximately 100-fold in red, slow-twitch muscle fiber in the Con + Ex group; and in the KD + Ex group, a KD contributed to this interesting up-regulation. In the context of exhaustive exercise, transcription levels of IL-6 increased significantly in the KD + Ex group, compared to the Con + Ex group in red, slow-twitch muscle. However, the effect was not observed in white, fast-twitch muscle. The result indicated that IL-6 gene expression exhibited a fiber type specificity."[432]

[B] The Ketogenic Diet only accelerates weight loss for the first one-two weeks, followed by pancreatic damage developing over the next 22 weeks. The weight loss that accompanies the first two week period must be considered partially glycogen, therefore it is essential that if lipolysis is your primary goal, beyond angiogenesis, or IL-6-based muscle growth, you must attempt to exhaust as much stored glycogen in your muscles as soon as you enter into a Ketogenic Diet, to facilitate ketosis and the lipolytic program as early as possible.
"<>High-fat, low-carbohydrate ketogenic diets (KD) are used for weight loss and for treatment of refractory epilepsy. Recently, short-time studies in rodents have shown that, besides their beneficial effect on body weight, KD lead to glucose intolerance and insulin resistance. However, the long-term effects on pancreatic endocrine cells are unknown. In this study we investigate the effects of long-term KD on glucose tolerance and β- and α-cell mass in mice. *Despite an initial weight loss*, KD did not result in weight loss after 22 wk.
<>Plasma markers associated with dyslipidemia and inflammation (cholesterol, triglycerides, leptin, monocyte chemotactic protein-1, IL-1β, and IL-6) were increased, and KD-fed mice showed signs of hepatic steatosis after 22 wk of diet. Long-term KD resulted in glucose intolerance that was associated with insufficient insulin secretion from

β-cells. After 22 wk, insulin-stimulated glucose uptake was reduced. A reduction in β-cell mass was observed in KD-fed mice together with an increased number of smaller islets. Also α-cell mass was markedly decreased, resulting in a lower α- to β-cell ratio.
<>Our data show that long-term KD causes dyslipidemia, a proinflammatory state, signs of hepatic steatosis, glucose intolerance, and a reduction in β- and α-cell mass, but no weight loss. This indicates that long-term high-fat, low-carbohydrate KD lead to features that are also associated with the metabolic syndrome and an increased risk for type 2 diabetes in humans."[433]

[C] The Ketogenic Diet promotes cardiac, and most likely, skeletal muscle angiogenesis.

"<>Blood vessel formation is dependent on metabolic adaptation in endothelial cells. Glucose and fatty acids are essential substrates for ATP and biomass production; however, the metabolism of other substrates remains poorly understood. Ketone bodies are important nutrients for cardiomyocytes during starvation or consumption of carbohydrate-restrictive diets. This raises the question whether cardiac endothelial cells would not only transport ketone bodies but also consume some of these to achieve their metabolic needs.
<>Here, we report that cardiac endothelial cells are able to oxidize ketone bodies and that this enhances cell proliferation, migration, and vessel sprouting. Mechanistically, this requires succinyl-CoA:3-oxoacid-CoA transferase, a key enzyme of ketone body oxidation. Targeted metabolite profiling revealed that carbon from ketone bodies got incorporated into tricarboxylic acid cycle intermediates as well as other metabolites fueling biomass production.
<>Elevation of ketone body levels by a high-fat, low-carbohydrate ketogenic diet transiently increased endothelial cell proliferation in mouse hearts. Notably, in a mouse model of heart hypertrophy, ketogenic diet prevented blood vessel rarefication. This suggests a potential beneficial role of dietary intervention in heart diseases."[433.1]

[D] Beta-hydroxybutyrate operates as an epigenetic modifier through Histone Deacetylase Inhibition and activates PGC1a.
"<>βOHB inhibits HDACs 1, 3 and 4 (class I and IIa) *in vitro* with an IC_{50} of 2–5 mM, suggesting that significant HDAC inhibition occurs even at the 1-2 mM serum concentrations that can be reached with fasting or ketogenic diet. Treating cultured cells with βOHB induces dose-dependent histone hyperacetylation, as does infusing βOHB into mice via osmotic pump."
↓ continued
"<>Much of our understanding of the biological effects of ketogenic diets come from studies in rodents. Ketogenic diets are a high-fat, high-energy state and so some of their effects on metabolism are similar to a typical high-fat or Western diet. Lean mice started on a ketogenic diet show increased fasting leptin , and hyperglycemia with insulin resistance, although basal insulin levels are lower. Ketogenic diets promote liver endoplasmic reticulum (ER) stress, similar to that seen in diabetic mice. There is strong

induction of hepatic genes involved in fatty acid oxidation, including acyl coA dehydrogenases and trifunctional enzyme components.
<>However, the ketogenic diet is unusual in that it simultaneously activates “fasting” pathways as well. For example, ketogenic diets suppress liver expression of fatty acid synthesis enzymes including stearoyl-CoA desaturase-1, whose induction by a high fat diet is important for development of metabolic syndrome. Instead, the “fasting regulator” genes PPARα and FGF21 are strongly induced, as is peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC1α), a master regulator of mitochondrial function.”[433.2]

[D2] Histone Deacetylase Inhibitors enhance hypertrophy through increased expression of Follistatin, which promotes muscle hypertrophy by improving myoblast fusion.

“<>Fusion of undifferentiated myoblasts into multinucleated myotubes is a prerequisite for developmental myogenesis and postnatal muscle growth. We report that deacetylase inhibitors favor the recruitment and fusion of myoblasts into preformed myotubes. Muscle-restricted expression of follistatin is induced by deacetylase inhibitors and mediates myoblast recruitment and fusion into myotubes through a pathway distinct from those utilized by either IGF-1 or IL-4. Blockade of follistatin expression by RNAi-mediated knockdown, functional inactivation with either neutralizing antibodies or the antagonist protein myostatin, render myoblasts refractory to HDAC inhibitors. Muscles from animals treated with the HDAC inhibitor trichostatin A display increased production of follistatin and enhanced expression of markers of regeneration following muscle injury.
<>These data identify follistatin as a central mediator of the fusigenic effects exerted by deacetylase inhibitors on skeletal muscles and establish a rationale for their use to manipulate skeletal myogenesis and promote muscle regeneration.”[434]

[E] The Ketogenic Diet (in this study, the fat comes from lard; high Palmitic acid > oleic > Linoleic acid, and moderate protein), likely through endogenous ketone production, enhances lifespan, and delays aging-induced strength losses.
It is interesting to note that this study used a diet high in Palmitic acid, which no doubt accelerates muscular and neurological aging. It becomes clearer with each study I read that even a diet high in nonessential fatty acids (Palmitic acid, Oleic acid, Stearic acid, etc.), as long as it is very low in carbohydrates, will delay aging, paradoxically to the detrimental effects of aforementioned fatty acids. I believe this is because of two reasons:

1. The body can convert dietary protein to glucose, whereas fatty acids are not capable of being formed from protein or carbohydrate digestion and must be obtained through diet alone, making carbohydrates non-essential macronutrients that can be used to facilitate insulins’ neurotrophic effects during youth, or to facilitate fast twitch muscle growth.

2. A low carbohydrate diet increases lipolysis, ketogenesis, and when paired with exercise, fatty acid oxidation, therefore rendering Palmitic acid and Oleic acid less toxic, especially if combined with chronic exercise.

"<>Calorie restriction, without malnutrition, has been shown to increase lifespan and is associated with a shift away from glycolysis toward beta-oxidation. The objective of this study was to mimic this metabolic shift using low-carbohydrate diets and to determine the influence of these diets on longevity and healthspan in mice. C57BL/6 mice were assigned to a ketogenic, low-carbohydrate, or control diet at 12 months of age and were either allowed to live their natural lifespan or tested for physiological function after 1 or 14 months of dietary intervention.
<>The ketogenic diet (KD) significantly increased median lifespan and survival compared to controls. In aged mice, only those consuming a KD displayed preservation of physiological function. The KD increased protein acetylation levels and regulated mTORC1 signaling in a tissue-dependent manner. This study demonstrates that a KD extends longevity and healthspan in mice."[434.1]

[F] The Ketogenic Diet promotes health and longevity primarily through increased Beta-hydroxybutyrate production, which in turn leads to epigenetic changes in the body, modulating Sirtuin expression and NAD+.
"<>The genetic information in the nucleus of eukaryotic cells is organized in a highly conserved structural polymer called chromatin. The basic unit of chromatin is the nucleosome. The nucleosome consists of 147 bp of DNA wrapped around an octamer of histones composed of two H3/H4 dimers and two H2A/H2B dimers. The dynamic and reversible modifications of histone proteins influence all DNA-based processes, including DNA packaging and chromatin compaction, nucleosome dynamics, and transcription. This process is regulated by several post-translational modifications, most of which occur within the amino terminal in histone tails.
<>Recently, ketone bodies have been shown to act as epigenetic modifiers that determine covalent modifications at key histones. These include lysine acetylation, methylation, and a novel epigenetic modification, lysine β-hydroxybutyrylation (Kbhb). Since Kbhb sites overlap with lysine residues, this novel histone modification integrates the classic histone lysine acetylation, methylation, and histone phosphorylation and ubiquitination, producing changes in the chromatin status. Generally, a genome-wide analysis (ChIP-swq) associated with transcriptional profiling revealed that the β-hydroxybutyrylation of histones is associated with active gene transcription. In liver from mice undergoing long-term fasting or streptozotocin-induced diabetic ketoacidosis, histone lysines susceptible to beta-hydroxybutyrylation were identified, including H1K168, H2AK5/K125, H2BK20, H3K4/K9/K14/K23, and H4K8/K12. In their study, the authors demonstrate that upregulated genes bearing the H3K9ac and H3K4me3 marks are different from those carrying the H3K9bhb mark, suggesting that histone Kbhb has different transcriptional-promoting functions than histone acetylation and methylation.
<>The effects of D-3-hydroxybutyric acid (BHB), one of the most abundant ketone bodies, on the establishment of histone tails' posttranslational modifications are very

controversial. Initially, BHB was considered an endogenous inhibitor of class I and class II histone deacetylases (HDACs); indeed, it has been shown that BHB treatment, in HEK293 cells or high levels of BHB produced by a subcutaneous pump delivery in C57BL6/J mice maintained on caloric restriction, produced a dose-dependent histone hyperacetylation, especially on lysine 9 and 14 of histone 3 (H3K9/K14). Other studies suggest that BHB only induces very marginal changes in the acetylation patterns, i.e., experiments conducted in various cell lines such as HEK293 cells, myotubes (L6), and endothelial cells (HMEC-1) showed that BHB administration had no effect on histone acetylation and did not inhibit histone deacetylase catalytic activity.
<>Understanding the effect of BHB on chromatin acetylation patterns is complicated by the NAD+/NADH ratio, which depends significantly on the presence of BHB or glucose.
<>BHB can substitute glucose as fuel; however, while glucose is able to produce four moles of NADH from NAD+, BHB is able to reduce only two moles of NAD+. The excess of the NAD+ resulting from the ketogenic diet modulates the activity of NAD+-dependent enzymes such as the Sirtuin proteins (SIRT1-7), which are involved in the deacetylation process.
Mice fed a ketogenic, low-carbohydrate diet showed a global increase in protein acetylation. These changes were accompanied by modifications in the regulation of rapamycin complex 1 (mTORC1), and in older animals, motor function and memory were preserved, and tumor incidence was lower. Similarly, obesity, higher mortality, and age-related memory loss were prevented in mice fed a cyclic (every two weeks) ketogenic diet. These effects have been linked to the downregulation of genes involved in fatty acid metabolism and the upregulation of Peroxisome Proliferator-Activated Receptor alpha (PPAR-) target genes, mechanisms that have been shown to be closely linked to epigenetic changes, at least in adipose tissue.
<>Further evidence for the role of epigenetic regulation by KD has been obtained in several mouse models. In mice exposed to hypobaric hypoxia, KD increased histone acetylation and rescued spatial memory impairment. Moreover, in Kmt2d(+/betaGeo), a mouse model with Kabuki syndrome, KD had the same effect as the administration of AR-42, a histone deacetylase inhibitor that promotes chromatin opening and rescues both the neurogenesis defect and hippocampal memory impairment. These effects are mediated via an increase in βOHB, which in turn modulates H3 acetylase and H3K4me3."[434.2]

[G] If you've previously gone on a Zero-K diet for months at a time, or if you like the idea of maintaining a Zero-K diet for longer than two weeks to maintain the ketogenic state, it may be possible to regenerate the Beta cells you have lost or will lose. Oral GABA use has been shown to both increase the mass and to proliferate Beta cells in human beings[1], but this effect appears to be nullified when combined with a high fat diet[2], although GABA appears to be anti-inflammatory through TREG activity[3], meaning that muscle tissue may be oversaturated with the cytokine IL-10 and TGF-b, which may disrupt myogenesis, therefore oral GABA use should be considered an Anti-Inflammatory Lipolytic compound, that can be used on a Ketogenic Diet, but in my opinion is best paired with a moderate-high carbohydrate Anti-Cycle, as strangely the

research does not show GABA promoting insulin resistance, even though it increases both GH release, and Insulin release, but this may be explained by increased insulin sensitivity owing to shorter but larger insulin spikes, due to increased Beta cell activity.

[1] "<>Type 1 diabetes (T1D) is an autoimmune disease characterized by insulitis and islet β-cell loss. Thus, an effective therapy may require β-cell restoration and immune suppression. Currently, there is no treatment that can achieve both goals efficiently. We report here that GABA exerts antidiabetic effects by acting on both the islet β-cells and immune system.
<>Unlike in adult brain or islet α-cells in which GABA exerts hyperpolarizing effects, in islet β-cells, GABA produces membrane depolarization and Ca2+ influx, leading to the activation of PI3-K/Akt–dependent growth and survival pathways. This provides a potential mechanism underlying our in vivo findings that GABA therapy preserves β-cell mass and prevents the development of T1D. Remarkably, in severely diabetic mice, GABA restores β-cell mass and reverses the disease.
<>Furthermore, GABA suppresses insulitis and systemic inflammatory cytokine production. The β-cell regenerative and immunoinhibitory effects of GABA provide insights into the role of GABA in regulating islet cell function and glucose homeostasis, which may find clinical application."[434.3]
[2] "<>γ-Aminobutyric acid (GABA) administration has been shown to increase β-cell mass, leading to a reversal of type 1 diabetes in mice. Whether GABA has any effect on β cells of healthy and prediabetic/glucose-intolerant obese mice remains unknown. In the present study, we show that oral GABA administration (ad libitum) to mice indeed increased pancreatic β-cell mass, which led to a modest enhancement in insulin secretion and glucose tolerance. However, GABA treatment did not further increase insulin-positive islet area in high fat diet-fed mice and was unable to prevent or reverse glucose intolerance and insulin resistance.
<>Mechanistically, whether in vivo or in vitro, GABA treatment increased β-cell proliferation. In vitro, the effect was shown to be mediated via the GABAA receptor. Single-cell RNA sequencing analysis revealed that GABA preferentially up-regulated pathways linked to β-cell proliferation and simultaneously down-regulated those networks required for other processes, including insulin biosynthesis and metabolism. Interestingly, single-cell differential expression analysis revealed GABA treatment gave rise to a distinct subpopulation of β cells with a unique transcriptional signature, including urocortin 3 (ucn3), wnt4, and hepacam2.
<>Taken together, this study provides new mechanistic insight into the proliferative nature of GABA but suggests that β-cell compensation associated with prediabetes overlaps with, and negates, its proliferative effects."[434.4]

[3] "<>Adipocyte and β-cell dysfunction and macrophage-related chronic inflammation are critical for the development of obesity-related insulin resistance and type 2 diabetes mellitus (T2DM), which can be negatively regulated by Tregs. Our previous studies and those of others have shown that activation of γ-aminobutyric acid (GABA) receptors

inhibits inflammation in mice. However, whether GABA could modulate high fat diet (HFD)-induced obesity, glucose intolerance and insulin resistance has not been explored. <>Here, we show that although oral treatment with GABA does not affect water and food consumption it inhibits the HFD-induced gain in body weights in C57BL/6 mice. Furthermore, oral treatment with GABA significantly reduced the concentrations of fasting blood glucose, and improved glucose tolerance and insulin sensitivity in the HFD-fed mice. More importantly, after the onset of obesity and T2DM, oral treatment with GABA inhibited the continual HFD-induced gain in body weights, reduced the concentrations of fasting blood glucose and improved glucose tolerance and insulin sensitivity in mice.
<>In addition, oral treatment with GABA reduced the epididymal fat mass, adipocyte size, and the frequency of macrophage infiltrates in the adipose tissues of HFD-fed mice. Notably, oral treatment with GABA significantly increased the frequency of CD4+Foxp3+ Tregs in mice.
<>Collectively, our data indicated that activation of peripheral GABA receptors inhibited the HFD-induced glucose intolerance, insulin resistance, and obesity by inhibiting obesity-related inflammation and up-regulating Treg responses in vivo. Given that GABA is safe for human consumption, activators of GABA receptors may be valuable for the prevention of obesity and intervention of T2DM in the clinic."[434.5]

[H] A major issue with obesity and a high fat ketogenic diet is the occurrence of Incomplete Beta-Oxidation, where Ceramides are formed due to Beta-Oxidation dysfunction. This Incompleteness can be countered in my hypothesis through high frequency, moderate intensity Endurance Training (+ PGC1a), but two far easier ways to prevent Incomplete Beta-Oxidation is firstly to avoid the consumption of long chain fatty acids (Palmitic, Oleic, Stearic, Linoleic), as stick with rapidly digestible ones such as those found in MCT oil, and the second option is through L-Carnitine supplementation, as Carnitine is necessary for long chain fatty acid transportation into mitochondria, and therefore is required for optimal fatty acid oxidation, especially if the fatty acids consumed dietarily are predominately long chain. Furthermore, it is a grave mistake that is obvious to me, but not to others, to assume that it healthy to consume excessive amounts of fatty acids, especially long chain fatty acids, on a low carbohydrate, or Zero-K Diet, when you are obese, and already suffering from metabolic dysfunction, as all that end up accomplishing is promoting intramuscular lipid accumulation. [See: Myokines: PGC1a [3.2]]

"<>In addition to its essential role in permitting mitochondrial import and oxidation of long chain fatty acids, carnitine also functions as an acyl group acceptor that facilitates mitochondrial export of excess carbons in the form of acylcarnitines. Recent evidence suggests carnitine requirements increase under conditions of sustained metabolic stress. <>Accordingly, we hypothesized that carnitine insufficiency might contribute to mitochondrial dysfunction and obesity-related impairments in glucose tolerance. Consistent with this prediction whole body carnitine diminution was identified as a

common feature of insulin-resistant states such as advanced age, genetic diabetes, and diet-induced obesity.
<>In rodents fed a lifelong (12 month) high fat diet, compromised carnitine status corresponded with increased skeletal muscle accumulation of acylcarnitine esters and diminished hepatic expression of carnitine biosynthetic genes. Diminished carnitine reserves in muscle of obese rats was accompanied by marked perturbations in mitochondrial fuel metabolism, including low rates of complete fatty acid oxidation, elevated incomplete beta-oxidation, and impaired substrate switching from fatty acid to pyruvate.
<>These mitochondrial abnormalities were reversed by 8 weeks of oral carnitine supplementation, in concert with increased tissue efflux and urinary excretion of acetylcarnitine and improvement of whole body glucose tolerance. Acetylcarnitine is produced by the mitochondrial matrix enzyme, carnitine acetyltransferase (CrAT). A role for this enzyme in combating glucose intolerance was further supported by the finding that CrAT overexpression in primary human skeletal myocytes increased glucose uptake and attenuated lipid-induced suppression of glucose oxidation. These results implicate carnitine insufficiency and reduced CrAT activity as reversible components of the metabolic syndrome."[434.6]

Heavy Metal Accumulation

Heavy Metals such as Lead, Arsenic, Cadmium, & Mercury are deposited systemically from dietary choices spanning over the course of our lifetimes. They associate with superficial aging due to tap water bathing & are toxic to muscle tissue by enhancing free radical production to pathological degrees, destabilizing the delicate cellular processes that make up myogenesis, and by promoting the release of muscle atrophy factors. It is important to realize that Iron deposition in the brains of the elderly is associated with Alzheimer's disease and other forms of neurodegeneration (read on).
The simplest way to counteract Heavy Metal-induced muscle toxicity or neurotoxicity is by increasing your intake of antioxidants, although the most effective Chelators are available through prescription only, there are three Chelating supplements and one modality of interest I have found. Indeed, although it is true that we will not be able to avoid the steady accumulation of heavy metals over time, unless nanobot technology progresses at a far faster rate, we can still mitigate a portion of this inescapable accumulative process through intelligent eating.

Forward:

"<>Background: Despite increasing concern regarding health problems as a result of environmental pollutants, no association of toxic heavy metals with sarcopenia has been demonstrated in the general population. We investigated the association of heavy metals, including lead, mercury and cadmium, with sarcopenia in the Korean population.

<>Methods: Participants included 344 males and 360 females older than 65 years. Measurements of blood lead, mercury and cadmium levels were performed. To evaluate the cumulative effect of the three heavy metals, subjects were categorized into quartiles. Results: Of 704 elderly persons (344 in males and 360 in females), prevalence of sarcopenia were 26.7% (92/344) in male and 7.5% (27/360) in female. Mean serum levels of lead in sarcopenia group were significantly higher than non-sarcopenia males (P=0.03). After adjustment for confounding factors, odds ratio for sarcopenia were increased with concentration category of lead (P=0.005 and P<0.001), mercury (P=0.001 and P<0.001) and cadmium (P=0.010 and P<0.001) in males and females, respectively. <>Conclusions: This study demonstrates that high levels of blood lead, mercury and cadmium increase the prevalence of sarcopenia in both genders of elderly populations."[435]

Over-the-counter Chelators

[A] Selenium for Mercury.

"<>Due to a long history of extensive mercury mining and smelting activities, local residents in Wanshan, China, are suffering from elevated mercury exposure. The objective of the present study was to study the effects of oral supplementation with selenium-enriched yeast in these long-term mercury-exposed populations. One hundred and three volunteers from Wanshan area were recruited and 53 of them were supplemented with 100 μg of organic selenium daily as selenium-enriched yeast while 50 of them were supplemented with the nonselenium-enriched yeast for 3 months. The effects of selenium supplementation on urinary mercury, selenium, and oxidative stress-related biomarkers including malondialdehyde and 8-hydroxy-2-deoxyguanosine were assessed. This 3-month selenium supplementation trial indicated that organic selenium supplementation could increase mercury excretion and decrease urinary malondialdehyde and 8-hydroxy-2-deoxyguanosine levels in local residents."[436]

[B] Modified Citrus Pectin (MCA) for intestinal Lead, Arsenic, & Cadmium.

This supplement is sadly understudied but in accordance with skepticism, I believe it to be a chelator, even if only for the intestinal tract. It would be wise for Beer, Wine, & Fruit Juice companies to add the chelator found within MCA—Rhamnogalacturonan-II, to their products as a prophylactic measure to protect their customers. (Pb = Lead).

[B] "<>This study was undertaken to evaluate the effect of modified citrus pectin (MCP) on the urinary excretion of toxic elements in healthy individuals. MCP is a reduced molecular weight pectin (weight-average molar mass = 15,400) that is mostly linear homogalacturonan with a 3.8% degree of esterification and approximately 10% rhamnogalacturonan II based on the presence of 2-keto-3-deoxy-octonic acid. Subjects

ingested 15 g of MCP (PectaSol, EcoNugenics Inc., Santa Rosa, California 95407) each day for 5 days and 20 g on day 6.
<>Twenty-four hour urine samples were collected on day 1 and day 6 for comparison with baseline. The urine samples were analysed for toxic and essential elements. In the first 24 h of MCP administration the urinary excretion of arsenic increased significantly (130%, $p < 0.05$). On day 6, urinary excretion was increased significantly for cadmium (150%, $p < 0.05$). In addition, lead showed a dramatic increase in excretion (560%, $p < 0.08$).
<>This pilot trial provides the first evidence that oral administration of MCP increases significantly the urinary excretion of toxic metals in subjects with a 'normal' body load of metals. It is suggested that systemic chelation of toxic metals by MCP may in part be attributable to the presence of rhamnogalacturonan II, which has been shown previously to chelate metals."[437]

[B2] "<>Recently, rhamnogalacturonan-II dimer (dRGII) has been isolated and characterized from apples and wine (Pellerin et al. 1996). dRGII is a complex pectic polysaccharide present in fruits and vegetables and also in fruit juices and wine. In vitro studies have shown that dRGII forms coordination complexes with di- and trivalent cations. We have also shown that the addition of unleaded dRGII to their diet helped further decrease Pb absorption and burden in rats. These data strongly suggest a potential detoxifying effect of dRGII, probably through chelation of dietary and endogenous Pb in the gastrointestinal tract. The aim of the present study was therefore to evaluate the potential detoxifying effect of different doses of dRGII after chronic Pb exposure in rats.
<>In conclusion, our findings show that dietary Pb, when bound to dRGII, is essentially unavailable for intestinal absorption. Consequently, Pb present in the form of dRGII chelates in fruits, vegetables and fruit juices is probably not available for absorption. However, our results show also that the addition of dRGII after Pb exposure was not effective in assisting the process of Pb detoxification in rats. Therefore, although the presence of dRGII in food may have a preventive action on Pb absorption, it seems unable to act as a curative agent in Pb poisoning."[438]

[B3] MCA may cause colitis or other gastrointestinal damage through being a source of Galacturonic Acid.

"<>Enteric pathogens sense the complex chemistry within the gastrointestinal tract to efficiently compete with the resident microbiota and establish a colonization niche. Here, we show that enterohaemorrhagic Escherichia coli and Citrobacter rodentium, its surrogate in a mouse infection model, sense galacturonic acid to initiate a multi-layered program towards successful mammalian infection. Galacturonic acid utilization as a carbon source aids the initial pathogen expansion.
<>The main source of galacturonic acid is dietary pectin, which is converted to galacturonic acid by the prominent member of the microbiota, Bacteroides thetaiotamicron. This is regulated by the ExuR transcription factor. However, galacturonic acid is also sensed as a signal through ExuR to modulate the expression of

the genes encoding a molecular syringe known as a type III secretion system, leading to infectious colitis and inflammation. Galacturonic acid acts as both a nutrient and a signal directing the exquisite microbiota-pathogen relationships within the gastrointestinal tract. This work highlights that differential dietary sugar availability influences the relationship between the microbiota and enteric pathogens, as well as disease outcomes."[439]

[C] EGCg for brain Iron chelation: If you are over the age of forty, I would suggest fasting for three days every year with water and consuming an EGCg extract in a dosing schedule of around 3-5g Grams every six hours to cleanse your brain of a portion of its Iron load, which accumulates in discrete brain regions over time and exerts toxic effects. Remember that EGCg binds to certain amino acids and therefore must be consumed on an empty stomach.

[C2] Regarding Iron accumulation during aging.

"<>The alteration of iron homeostasis related to the aging process is responsible for increased iron levels, potentially leading to oxidative cellular damage. Iron is modulated in the Central Nervous System in a very sensitive manner and an abnormal accumulation of iron in the brain has been proposed as a biomarker of neurodegeneration. However, contrasting results have been presented regarding brain iron accumulation and the potential link with other factors during aging and neurodegeneration. Such uncertainties partly depend on the fact that different techniques can be used to estimate the distribution of iron in the brain, e.g., indirect (e.g., MRI) or direct (post-mortem estimation) approaches.
<>Furthermore, recent evidence suggests that the propensity of brain cells to accumulate excessive iron as a function of aging largely depends on their anatomical location. This review aims to collect the available data on the association between iron concentration in the brain and aging, shedding light on potential mechanisms that may be helpful in the detection of physiological neurodegeneration processes and neurodegenerative diseases such as Alzheimer's disease."[439.1]

[C3] "<>Brain iron dysregulation and its association with amyloid precursor protein (APP) plaque formation are implicated in Alzheimer's disease (AD) pathology and so iron chelation could be considered a rational therapeutic strategy for AD. Here we analyzed the effect of the main polyphenol constituent of green tea, (-)-epigallocatechin-3-gallate (EGCG), which possesses metal-chelating and radical-scavenging properties, on the regulation of the iron metabolism-related proteins APP and transferrin receptor (TfR). <>EGCG exhibited potent iron-chelating activity comparable to that of the prototype iron chelator desferrioxamine, and dose dependently (1-10 microm) increased TfR protein and mRNA levels in human SH-SY5Y neuroblastoma cells. Both the immature and full-length cellular holo-APP were significantly reduced by EGCG, as shown by two-dimensional gel electrophoresis, without altering APP mRNA levels, suggesting a post-transcriptional action."[440]

Chelation Modalities

Sweating (Hyperthermia)

A wonderful and inexpensive antiaging strategy, aside from the myogenic benefits, imagine how young you will look by frequently excreting a portion of the heavy metals lodged in your facial tissue? I predict the future of antiaging face therapies will be topical hyperthermia therapy. For now, if you are a woman obsessed with superficial aging, why not put a heat pad on your face for an hour every night?

"<>Arsenic, cadmium, lead, and mercury exposures are ubiquitous. These toxic elements have no physiological benefits, engendering interest in minimizing body burden. The physiological process of sweating has long been regarded as "cleansing" and of low risk. Reports of toxicant levels in sweat were sought in Medline, Embase, Toxline, Biosis, and AMED as well as reference lists and grey literature, from inception to March 22, 2011. Of 122 records identified, 24 were included in evidence synthesis. Populations, and sweat collection methods and concentrations varied widely.
<>In individuals with higher exposure or body burden, sweat generally exceeded plasma or urine concentrations, and dermal could match or surpass urinary daily excretion. Arsenic dermal excretion was severalfold higher in arsenic-exposed individuals than in unexposed controls. Cadmium was more concentrated in sweat than in blood plasma. Sweat lead was associated with high-molecular-weight molecules, and in an interventional study, levels were higher with endurance compared with intensive exercise. Mercury levels normalized with repeated saunas in a case report.
<>Sweating deserves consideration for toxic element detoxification. Research including appropriately sized trials is needed to establish safe, effective therapeutic protocols."[441]

Air Quality

The quality of our ambient air is a forgotten factor that plays a major role in pathological aging with the most relevant particles in our air that affect our health being 2.5 Microns (PM2.5) or smaller, as they absorb to a greater extent into our lung tissue. It is an unwise idea to purchase a HEPA air purifier that uses a fiberglass filter, which is why I use (although it may change one day), **Polypropylene** filter HEPA air purifiers by Sharp (Model FPF30UH), as it is possible that fiberglass HEPA air filters (Honeywell) shed their respective particles during activate use, which would make them toxic to the lungs yet beneficial to the heart, as the ambient air pollution would decrease for the tradeoff of inhaled and accumulative fiberglass particulate.

Consider also buying a cheap laser air particle counter off amazon to test your house and city's air quality every week. Ideally, you will want to keep your indoor PM2.5 level at a **15** or lower for optimal health, in my opinion.

There are many different pollutants that reside in the air we breathe in each day; the most toxic air pollution can be found in metropolitan areas where there are factories in operation and where vehicles are commonplace on streets and highways, because of this, even if you turn your home into a filtered air paradise, you will still be aging your body every time you exit your home. The aforementioned point brings me to the conclusion that the more polluted your city, the greater need it will be for you to stay on an Anti-Cycle to reduce the pathological inflammation stimulated through inhalation.

Chlorine is a rather unknown air pollutant[441.1] that causes an inflammatory reaction in the lungs, you should therefore be cautious of spending too much time in hyper chlorinated public pools, although I believe water resistance training is an underappreciated way to Warmup and to condition muscles.

[A] "<>The impacts of ambient PM2.5 on public health have become great concerns worldwide, especially in the developing countries. Epidemiological and toxicological studies have shown that PM2.5 does not only induce cardiopulmonary disorders and/or impairments, but also contributes to a variety of other adverse health effects, such as driving the initiation and progression of diabetes mellitus and eliciting adverse birth outcomes.
<>Of note, recent findings have demonstrated that PM2.5 may still pose a hazard to public health even at very low levels (far below national standards) of exposure. The proposed underlying mechanisms whereby PM2.5 causes adverse effects to public health include inducing intracellular oxidative stress, mutagenicity/genotoxicity and inflammatory responses."[442]

[A2] PM2.5 air pollution may cause strokes.
"<>Background: Stroke is one of the world's leading causes of death. Many studies have checked the relationship between short-term exposure to particulate matter (PM) and stroke, but few have focused on the effect of long-term exposure to PM2.5 (particulate matters with an aerodynamic diameter of ≤2.5 μm). This study aimed to quantitatively examine the relationship of long-term exposure to PM2.5 with stroke incidence and mortality.
<>Methods: We identified relevant studies by searching the PubMed, EMBASE and MEDLINE. After the systematical review of pertinent studies, random-effect meta-analysis was conducted to investigate the association between long-term exposure to PM2.5 and stroke.
<>Results: Our meta-analysis included 16 cohort studies with more than 2.2 million people and above 49 149 endpoint events (incident stroke and death from stroke). The pooled hazard ratio (HR) for each 5 μg/m3 increment in PM2.5 was 1.11 (95% CI: 1.05, 1.17) (CI for confidence interval) for incidence of stroke and 1.11 (95% CI:1.05, 1.17) for mortality of stroke. In the region-specific analysis, significant association between PM2.5 and incidence of stroke was found in North America (HR=1.09, 95% CI:1.05, 1.14) and Europe (HR=1.07, 95% CI:1.05, 1.10), while the pooled result of Asia showed no significance (HR=2.31, 95% CI:0.49, 10.95). <>Conclusions: Long-term exposure to PM2.5 is an important risk factor for stroke. Since air quality is intimately related to everyone, policies aimed at reducing particulate matters will benefit public health a lot."[443]

[A3] PM2.5 air pollution causes lung cancer & cardiovascular disease.

"<>Background: Although a number of studies have reported on the health effects of fine particulate matter (PM2.5) exposure, particularly in North American and European countries as well as China, the evidence about intermediate to high levels of PM2.5 exposures is still limited. We aimed to investigate the associations between long-term exposure to PM2.5 and risk of cardiopulmonary disease incidence in Taiwan with intermediate levels of PM2.5 exposure.

<>Methods: A cohort of Taiwanese adults, who participated in the 2001, 2005, 2009 and 2013 National Health Interview Surveys, was followed through 2016 to identify cardiopulmonary disease onset. Exposure to PM2.5 was estimated by incorporating a widespread monitoring network of air quality monitoring stations and microsensors. We used time-dependent Cox regression models to examine the associations between the PM2.5 exposures and health outcomes, adjusting for individual characteristics and ecological covariates. The natural cubic spline functions were used to explore the non-linear effects of the PM2.5 exposure.
<>Results: A total of 62 694 adults from 353 towns were enrolled. Each 10-μg/m3 increase in 5-year average exposure to PM2.5 was associated with a 4.8% increased risk of incident ischaemic heart disease (95% CI: -3.3, 13.6), 3.9% increased risk of incident stroke (95% CI: -2.9, 11.1), 6.7% increased risk of incident diabetes (95% CI: 1.1, 12.7), 15.7% increased risk of incident lung cancer (95% CI: -0.9, 35.1) and 11.5% increased risk of incident chronic obstructive pulmonary disease (95% CI: -0.8, 25.2). The concentration-response curve showed that there was no statistical evidence of non-linearity for most of the disease outcomes except for ischaemic heart disease (P for non-linearity = 0.014).
<>Conclusions: Long-term exposure to intermediate levels of ambient PM2.5 was associated with cardiopulmonary health outcomes. Our study adds value to future application and national burden of disease estimation in evaluating the health co-benefits from ambient air pollution reduction policy in Asian countries."[443.1]

[A4] PM2.5 air pollution accelerates adipogenesis and promotes muscle atrophy.

"<>Loss of skeletal muscle mass is common with aging and can cause morbidity and mortality in the elderly. The effects of particulate air pollution on skeletal muscle mass is not known. The study aims to assess the chronic effects of ambient fine particulates (PM2.5) on the body composition of the elderly. From October 2015 to November 2016, a cross-sectional survey on 530 elderly (age > = 65 years) was conducted in the Taipei Basin, Taiwan. The body composition was measured by bioelectrical impedance analysis (InBody 120).
<>One year exposure to air pollution was estimated using the Kriging method at the participant's residence. Multiple linear regression analysis, after adjustments for demographics and co-pollutants, was used to examine the effects of PM2.5 on body composition indices and force of handgrip. Changes in body composition for an interquartile (1.4 μm/m3) increase in PM2.5 concentration included a 0.4 kg (95% confidence interval (CI): −0.31, −0.58; p < 0.0001) decrease in skeletal muscle mass (2.0%) and a 0.7 kg (95% CI: 0.47, 0.91; p < 0.0001) increase in body fat mass (3.6%). While PM2.5 reduced fat free mass in the upper extremities and trunk, but not in the lower extremities, it increased body fat mass in the three parts. There was no significant effect of PM2.5 on handgrip force.
<>Higher physical activity (versus lower than median) was associated with less detrimental effect of PM2.5 on skeletal muscle mass and body fat mass (p values for interaction term: 0.009 and 0.013, respectively). Long-term PM2.5 exposure is associated

with decreased skeletal muscle mass and increased body fat mass in the elderly, which can be ameliorated by physical activity."[443.2]

[A5] PM2.5 air pollution promotes skin aging.

"<>Traffic-related air pollution is known to be associated with skin aging manifestations. We previously found that the use of fossil fuels was associated with skin aging, but no direct link between indoor air pollutants and skin aging manifestations has ever been shown. Here we directly measured the indoor PM2.5 exposure in 30 households in Taizhou, China. Based on the directly measured PM2.5 exposure and questionnaire data of indoor pollution sources, we built a regression model to predict the PM2.5 exposure in larger datasets including an initial examination group (N = 874) and a second examination group (N = 1003). We then estimated the association between the PM2.5 exposure and skin aging manifestations by linear regression.
<>In the initial examination group, we showed that the indoor PM2.5 exposure levels were positively associated with skin aging manifestation, including score of pigment spots on forehead (12.5% more spots per increase of IQR, P-value 0.0371), and wrinkle on upper lip (7.7% more wrinkle on upper lip per increase of IQR, P-value 0.0218). The results were replicated in the second examination group as well as in the pooled dataset. Our study provided evidence that the indoor PM2.5 exposure is associated with skin aging manifestation in a Chinese population."[443.3]

[B] Cooking Oil Fumes (Cooking Oil Fume Volatile Organic Compounds) are hazardous to lung health, making it necessary to avoid cooking foods with large amounts of oils added, and highlighting the possible deleterious effects of working in restaurants. Sadly, HEPA Air Purifiers are not able to filter VOC's, making this issue one that may never be resolved.

"<>Background: As cooking is an essential part of people's daily life, cooking oil fumes (COF) has been recognized as one of the major indoor air pollutant. Mounting epidemiological evidence has indicated that COF exposure is significantly associated with an increased risk of various health effects including lung cancer, but toxicological studies are very limited.
<>Objectives: We conduct a systematic study to provide toxicological evidence of COF exposure on the lungs, to examine the underlying toxicological mechanism, and to suggest intervention measures to mitigate this toxicity.
<>Methods: A total 96 female rats were randomly divided into control groups, COF exposure groups (0.2, 2, 20 mg/kg) and vitamin E protection groups, receiving appropriate treatment for 30 days. First we measured airway hyperresponsiveness (AHR) followed by a lung histological analysis to investigate the toxicological effects of COF. We next analyzed the biomarkers of oxidative stress, inflammation, and apoptosis to examine the underlying toxicological mechanism, and finally we investigated the protective effects of vitamin E against the toxicity of COF.

<>Results: AHR measurement indicated that the airway resistance increased with the COF dose and the lung histological assay showed narrowing of the airway lumen, which provided evidence of the toxicological effects of COF. The biomarkers of oxidative stress (ROS and MDA), pro-inflammation (TNF-α and IL-1β), and apoptosis (NF-κB and Caspase-3) were all significantly increased with COF dose. We observed that above toxicological effects and biomarker levels induced by COF were significantly ameliorated after administration of VE.
<>Conclusion: The toxicity of cooking oil fumes on the lungs is clear from the evidence and mechanism, and can be ameliorated by vitamin E. We suggested that oxidative stress may be primarily responsible for the observed cooking oil fumes-induced toxicity."[443.4]

[B2] Air Frying food (with oil) is likely to contribute to greater ambient air pollution than traditional baking. I do understand the whole selling point of Air Fryers is the lessened use of oils on food, but this doesn't defeat the study, as even Air Frying fatty meats devoid of added cooking oils is likely to produce air contamination.

"<>Air frying has become a popular cooking method for domestic cooking, but the level of released indoor air pollutants is poorly understood. In this work, we compared particle and gas phase emission factors (EF) and particle size distributions between cooking with a domestic air fryer and a pan for a variety of foods. The PM10 EFs of air frying chicken wings and breast were higher than pan cooking by a factor of 2.1 and 5.4, respectively. On the other hand, a higher PM10 emission factor from air frying can be achieved by increasing the amount of oil to levels similar to or above those from pan-frying for French fries and asparagus.
<>We propose that higher temperature and greater turbulence lead to higher PM10 EFs for cooking with the air fryer compared with the pan for the same mass of oil added. EFs of volatile organic compounds (VOCs) are also generally higher for cooking with the air fryer compared with the pan: 2.5 times higher for French fries and 4.8 times higher for chicken breast. Our study highlights the potential risk of higher indoor PM10 levels associated with domestic air frying under certain cases and proposes possible mitigation measures."[443.5]

Fructose, Sucrose, & Advanced Glycation End Products

Dietary Fructose, being the secondary primordial addiction, accelerates cellular aging due to the formation of Advanced Glycation End Products (AGEs), which activate the Receptor for Advanced Glycosylation End-products (RAGE), which stimulates a cascade of inflammatory factor release (TNF-a / IL-1B), and this is the result of fructose molecules binding to proteins and lipids. AGEs accumulate in our bodies over time causing neurodegeneration, insulin resistance, wrinkles, autoimmune diseases, and muscle atrophy. Although AGEs are *inflammatory* and may promote mitochondrial function (and possibly angiogenesis) in very low concentrations, they are not a required

factor in the processes of efficient myogenesis, lipolysis, or angiogenesis, and because they *accumulate* in the body, they are dangerous and should be purposefully inhibited from forming through supplement use or special dietary restrictions. I have argued against chronic fructose consumption for years with people who mistakenly believe that *common fruit* (not Wild Blueberries) consumption is healthy, including super sweet fruit smoothies and juices, but now I have evidence to support my claims.

[A] AGE's cause muscle atrophy.

"<>Diabetic myopathy, a less studied complication of diabetes, exhibits the clinical observations characterized by a less muscle mass, muscle weakness and a reduced physical functional capacity. Accumulation of advanced glycation end-products (AGEs), known to play a role in diabetic complications, has been identified in ageing human skeletal muscles. However, the role of AGEs in diabetic myopathy remains unclear. <>Here, we investigated the effects of AGEs on myogenic differentiation and muscle atrophy in vivo and in vitro. We also evaluated the therapeutic potential of alagebrium chloride (Ala-Cl), an inhibitor of AGEs. Muscle fibre atrophy and immunoreactivity for AGEs, Atrogin-1 (a muscle atrophy marker) and phosphorylated AMP-activated protein kinase (AMPK) expressions were markedly increased in human skeletal muscles from patients with diabetes as compared with control subjects.
<>Moreover, in diabetic mice we found increased blood AGEs, less muscle mass, lower muscular endurance, atrophic muscle size and poor regenerative capacity, and increased levels of muscle AGE and receptor for AGE (RAGE), Atrogin-1 and phosphorylated AMPK, which could be significantly ameliorated by Ala-Cl. Furthermore, in vitro, AGEs (in a dose-dependent manner) reduced myotube diameters (myotube atrophy) and induced Atrogin-1 protein expression in myotubes differentiated from both mouse myoblasts and primary human skeletal muscle-derived progenitor cells.
<>AGEs exerted a negative regulation of myogenesis of mouse and human myoblasts. Ala-Cl significantly inhibited the effects of AGEs on myotube atrophy and myogenesis. We further demonstrated that AGEs induced muscle atrophy/myogenesis impairment via a RAGE-mediated AMPK-down-regulation of the Akt signalling pathway. Our findings support that AGEs play an important role in diabetic myopathy, and that an inhibitor of AGEs may offer a therapeutic strategy for managing the dysfunction of muscle due to diabetes or ageing."[444]

[B] Sugar (Sucrose) facilitates fast twitch fiber growth independently of insulin.

"<>Skeletal muscle protein synthesis is elevated in neonates in part due to an enhanced response to the rise in insulin and amino acids after eating. In vitro studies suggest that glucose plays a role in protein synthesis regulation. To determine whether glucose, independently of insulin and amino acids, is involved in the postprandial rise in skeletal muscle protein synthesis, pancreatic-substrate clamps were performed in neonatal pigs. Insulin secretion was inhibited with somatostatin and insulin was infused to reproduce

fasting or fed levels, while glucose and amino acids were clamped at fasting or fed levels. Fractional protein synthesis rates and translational control mechanisms were examined. <>Raising glucose alone increased protein synthesis in fast-twitch glycolytic muscles but not in other tissues. The response in muscle was associated with increased phosphorylation of protein kinase B (PKB) and enhanced formation of the active eIF4E.eIF4G complex but no change in phosphorylation of AMP-activated protein kinase (AMPK), tuberous sclerosis complex 2 (TSC2), mammalian target of rapamycin (mTOR), 4E-binding protein-1 (4E-BP1), ribosomal protein S6 kinase (S6K1), or eukaryotic elongation factor 2 (eEF2).
<>Raising glucose, insulin, and amino acids increased protein synthesis in most tissues. The response in muscle was associated with phosphorylation of PKB, mTOR, S6K1, and 4E-BP1 and enhanced eIF4E.eIF4G formation. The results suggest that the postprandial rise in glucose, independently of insulin and amino acids, stimulates protein synthesis in neonates, and this response is specific to fast-twitch glycolytic muscle and occurs by AMPK- and mTOR-independent pathways."[445]

[C] Hyperglycemia reduces angiogenesis, although it's safe to say that whereas low glucose conditions (+IL-6) facilitate muscle growth (especially slow twitch), high glucose conditions (glycogen sparing) facilitate fast twitch fiber growth.

"<>Diabetes is associated with abnormal angiogenesis. Increased angiogenesis contributes to severe forms of diabetic retinopathy, but angiogenesis is decreased in response to myocardial ischemia in diabetic patients. We evaluated the direct effect of hyperglycemia on angiogenesis in the chicken chorioallantoic membrane assay, a model of active neoangiogenesis. Hyperglycemia, lasting up to 7 days, was induced in 7-day-old chick embryos by a single intravitellus glucose injection. Control embryos received either water (volumic control) or mannitol (osmotic control). Hyperglycemia decreased angiogenesis in this model from the 5th day on. The pattern and expression level of the main vascular growth factors' genes were not altered by hyperglycemia, as assessed by in situ hybridization and semiquantitative RT-PCR. As early as 2 days after hyperglycemia was induced, an increased apoptosis of endothelial cells and pericytes was detected by transferase-mediated deoxyuridine triphosphate nick-end labeling assay and electron microscopy.
<>In the meantime, endothelial cell proliferation was decreased, as assessed by incorporation of bromo-deoxyuridine. Hyperglycemia can therefore impair angiogenesis without altering the expression level of vascular growth factors through induction of apoptosis and decreased proliferation of endothelial cells."[446]

[D] Oral Glucose consumption reduces Testosterone, making the Ketogenic Diet more anabolic for men than women.

"<>Objective: This study examines the physiological impact of a glucose load on serum testosterone (T) levels in men with varying glucose tolerance (GT).

<>Patients and methods: 74 men (19-74 years, mean 51·4 ± 1·4 years) underwent a standard 75-g oral glucose tolerance test with blood sampling at 0, 30, 60, 90 and 120 min. Fasting serum glucose, insulin, total T (and calculated free T), LH, SHBG, leptin and cortisol were measured.
<>Results: 57% of the men had normal GT, 30% had impaired GT and 13% had newly diagnosed type 2 diabetes. Glucose ingestion was associated with a 25% decrease in mean T levels (delta = -4·2 ± 0·3 nm, P < 0·0001). T levels remained suppressed at 120 min compared with baseline (13·7 ± 0·6 vs 16·5 ± 0·7 nm, P < 0·0001) and did not differ across GT or BMI. Of the 66 men with normal T levels at baseline, 10 (15%) had levels that decreased to the hypogonadal range (<9·7 nm) at one or more time points. SHBG, LH and cortisol levels were unchanged. Leptin levels decreased from baseline at all time points (P < 0·0001).
<>Conclusions: Glucose ingestion induces a significant reduction in total and free T levels in men, which is similar across the spectrum of glucose tolerance. This decrease in T appears to be because of a direct testicular defect, but the absence of compensatory changes in LH suggests an additional central component. Men found to have low nonfasting T levels should be re-evaluated in the fasting state."[446.1]

!!CAUTION!! Fructose !!CAUTION!!

Fructose is the most toxic sugar by way of three primary mechanisms:

1. Chronic AGE formation.

2. Cortisol release.

3. Microbiome derangement. [See: Muscle Lipid Accumulation]

[1] "<>Fructose is a ketohexose and sweetest among all the natural sugars.
Like other reducing sugars, it reacts readily with the amino- and nucleophilic groups of proteins, nucleic acids and other biomolecules resulting in glycation reactions. The non-enzymatic glycation reactions comprise Schiff base formation, their Amadori rearrangement followed by complex and partly incompletely understood reactions culminating in the formation of Advance Glycation End products (AGEs).
<>The AGEs are implicated in complications associated with diabetes, cardiovascular disorders, Parkinson's disease, etc. Fructose is highly reactive and forms glycation products that differ both in structure and reactivity as compared to those formed from glucose. Nearly all tissues of higher organisms utilize fructose but only a few like the ocular lens, peripheral nerves erythrocytes and testis have polyol pathway active for the synthesis of fructose. Fructose levels rarely exceed those of glucose but, in tissues that operate the polyol pathway, its concentration may rise remarkably during diabetes and related disorders.
<>Diet contributes significantly to the body fructose levels however, availability of technologies for the large scale and inexpensive production of fructose, popularity of high fructose syrups as well as the promotion of vegetarianism have resulted in a

remarkable increase in the consumption of fructose. In vivo glycation reactions by fructose, therefore, assume remarkable significance. The review, therefore, aims to highlight the uniqueness of glycation reactions with fructose and its role in some pathophysiological situations."[447]

[2] "<>Traditionally, the leading hypothesis regarding the development of obesity involves caloric imbalance, whereby the amount of calories consumed exceeds the amount of calories burned which causes obesity. Another hypothesis for why we get fat has surfaced in the last decade which is the idea that the overconsumption of added sugars and refined carbohydrates induce insulin resistance and high insulin levels causing obesity. While insulin is a fat-storing hormone, this hypothesis does not explain visceral adiposity, or why certain people are found to have fat stored in and around their organs. We propose a new mechanism for body fattening, particular visceral adiposity.
<>This hypothesis involves the overconsumption of fructose, which leads to inflammation in all cells that metabolize it rapidly. When fructose is metabolized in subcutaneous adipocytes, the subsequent inflammation leads to an increase in intracellular cortisol in order to help squelch the inflammation. Unfortunately, the increase in intracellular cortisol leads to an increased flux of fatty acids out of the subcutaneous adipocytes allowing more substrate for fat storage into visceral fat tissue. Moreover fructose-induced inflammation in the liver also leads to increased intracellular cortisol via an upregulation of 11-B hydroxysteroid dehydrogenase type 1 causing increased fat storage in the liver (i.e., fatty liver).
<>In essence, the fructose-induced inflammatory cortisol response causes "thin on the outside, fat on the inside" (TOFI). Furthermore, fructose in the brain, either from fructose uptake via the blood brain barrier or endogenous formation from glucose via the polyol pathway stimulates an increased release of cortisol causing hepatic gluconeogenesis leading to overall insulin resistance and further body fattening. This review paper will discuss in detail the hypothesis that fructose-induced inflammation and cortisol activation causes visceral adiposity." [447]

AGE Inhibitors

Alpha-lipoic acid (ALA)

[A] ALA is a great AGE inhibitor.

"<>The present study investigates the antiglycating effect of alpha-lipoic acid (LA) in high fructose-fed rats in vivo and its potential to inhibit the process of glycation in vitro. In addition, the effect of LA on glucose utilisation in rat diaphragm was also studied. Rats fed a high fructose diet (60% total calories) were administered with 35 mg/kg b.w, lipoic acid (LA) intraperitoneally for 20 days.
<>The effects of LA on plasma glucose, fructosamine, protein glycation and glycated haemoglobin in high fructose rats and on in vitro glycation were studied. In vitro utilization of glucose was carried out in normal rat diaphragm in the presence and

absence of insulin in which LA was used as an additive. The contents of glucose, glycated protein, glycated haemoglobin and fructosamine were significantly lowered on LA administration to high fructose-fed rats. LA prevented in vitro glycation and the accumulation of advanced glycation end products. Further LA enhanced glucose utilization in the rat diaphragm. This effect was additive to that of insulin and did not interfere with the action of insulin. The findings provide evidence for the therapeutic utility of lipoic acid in diabetes and its complications."[448]

[A2] Alpha-lipoic acid is anti-aging through promoting collagen synthesis.

"<>The collapse of collagenous networks with aging results in comprehensive changes in the functional properties of skin. α-Lipoic acid (LA) is known to possess beneficial effects against skin aging, effects often presumed to be its antioxidant potential. However, the effects of LA on fibrillogenesis in dermal fibroblasts have not been adequately assessed. In this study, we demonstrated for the first time that LA enhances the biosynthesis of new collagen in normal human dermal fibroblasts (NHDFs). By using a quantitative dye-binding method and immunochemical approaches, we showed that LA effectively increased the expression and subsequently the deposition of type I collagen in NHDFs. LA also facilitated the expression of a collagen-processing enzyme, prolyl-4-hydroxylase, pointing to the existence of a posttranslational mechanism among the LA-mediated effects on collagen synthesis.
<>In addition, we determined that both Smad 2/3 were rapidly phosphorylated by treatment with LA within 30 min, indicating that LA enhances type I collagen synthesis through the activation of Smad signaling. Pretreatment of SB431542, a specific transforming growth factor-β (TGF-β) receptor type I (TβRI) kinase inhibitor, blocked LA-mediated Smad 2/3 phosphorylations and both type I collagen and prolyl-4-hydroxylase expression, suggesting that LA-mediated cell responses are regulated by TβRI kinase-dependent pathway. Levels of TGF-β secretion after 4 hr of treatment with LA were not remarkably elevated, indicating that LA may be able to mimic TGF-β-mediated cell response. The study results produced new insights into the molecular pharmacology of LA in NHDFs, with potential applications in the treatment of aging skin."[449]

[B] Alpha-lipoic acid promotes lifespan extension, likely through *ROS-induced* mitochondrial biogenesis.

"<>α-lipoic acid increased survival in five of six trials at a concentration of 1mM (log rank test; $p \leq 0.0043$). Median lifespan was increased by on average 21%."[449.1]

[C] Alpha-lipoic acid promotes lipolysis.

"<>Purpose: alpha-lipoic acid is an essential cofactor for mitochondrial respiratory enzymes that improves mitochondrial function. We previously reported that alpha-lipoic

acid markedly reduced body weight gain in rodents. The purpose of this study was to determine whether alpha-lipoic acid reduces body weight in obese human subjects.
<>Methods: in this randomized, double-blind, placebo-controlled, 20-week trial, 360 obese individuals (body mass index [BMI] ≥ 30 kg/m(2) or BMI 27-30 kg/m(2) plus hypertension, diabetes mellitus, or hypercholesterolemia) were randomized to alpha-lipoic acid 1200 or 1800 mg/d or placebo. The primary end point was body weight change from baseline to end point.
<>Results: the 1800 mg alpha-lipoic acid group lost significantly more weight than the placebo group (2.1%; 95% confidence interval, 1.4-2.8; P<.05). Urticaria and itching sensation were the most common adverse events in the alpha-lipoic acid groups, but these were generally mild and transient.
<>Conclusion: alpha-lipoic acid 1800 mg/d led to a modest weight loss in obese subjects. Alpha-lipoic acid may be considered as adjunctive therapy for obesity."[449.2]

[C2] Alpha-lipoic acid promotes lipolysis through paradoxically enhancing ROS which apparently results in reduced Glycogen storage, which must ultimately culminate in increases to AMPK expression. Interestingly, this study shows that Insulin reduces ROS.

"<>Alpha-Lipoic acid (LA) is currently being investigated as a glucose-lowering agent for diabetes control; it is also considered a powerful dietary antioxidant. The objective of this study was to investigate the fate of glucose in isolated rat muscles incubated with LA and determine its effects on intramuscular redox status. Rat soleus muscles were incubated for up to 60 min with 2.4 mmol/L LA in the presence or absence of insulin. Intramuscular concentrations of LA were evaluated (uptake and reduction), and glycogen synthesis, glucose oxidation, intramuscular reactive oxygen species (ROS) production and mitochondrial membrane potential investigated.
<>Insulin enhanced glycogen synthesis, whereas LA decreased rates by >50%. LA elevated ROS production and in combination with t-butylhydroperoxide, an oxidant, additively inhibited glycogen synthesis rates by 80%. Insulin acted as an antioxidant and attenuated ROS production by 30%. LA uncoupled the mitochondria and accelerated glucose oxidation 1.5-fold relative to the control.
<>The glycogen synthesis pathway was found to be dependent on mitochondrial function because treatment with mitochondrial inhibitors eliminated the majority of glycogen synthesis.
<>These data show that in this model, LA acts as a mild prooxidant, causing mitochondrial uncoupling and inhibition of glycogen synthesis. It appears that LA regulates glucose metabolism in the muscle differently than insulin."[449.3]

[D] Lipoic acid increases ERK1/2, but more importantly Caspase-3, making it a potentially damaging agent towards blood vessels, but capable of *killing fat cells*. [See: Important Inflammatory Factors: Caspase-3]

"<>Endothelial cell apoptosis contributes to atherosclerosis and may be exacerbated by oxidative stress. Results from clinical trials using antioxidant supplementation are

equivocal and could be enhanced by antioxidants with additional non-antioxidant properties such as alpha -lipoic acid and alpha -tocopherol. The aim of this study was to investigate the effects of these antioxidants on cytoprotective pathways and endothelial apoptosis.
<>Endothelial cells were incubated with alpha -lipoic acid and alpha -tocopherol, alone or in combination, prior to incubation with H(2)O(2) or staurosporine. alpha -lipoic acid pre-treatment alone increased caspase-3 activity in a dose-dependent manner. Both H(2)O(2) and staurosporine increased DNA fragmentation and caspase-3 activity and pre-treatment of cells with alpha -lipoic acid and/or alpha -tocopherol failed to prevent stress-induced apoptosis. Neither antioxidant treatments nor apoptotic inducers alone altered expressions of Bcl-2, Bax, HSP70 or pERK1/2 or pJNK.
<>Alpha-lipoic decreased pERK2 in staurosporine-treated cells in a dose-dependent manner. These findings indicate that pre-incubation with alpha-lipoic acid and alpha -tocopherol, alone or in combination, does not protect against oxidative- or non-oxidative-induced apoptosis in endothelial cells.
<>Moreover, we have demonstrated a non-antioxidant, dose-dependent role of alpha -lipoic acid in caspase-3 and ERK2 activation. These data provide an insight and indicate caution in the use of high doses of alpha -lipoic acid as an antioxidant."[449.4]

[E] MRSA releases Lipoic Acid to enhance virulence. Yes, that's right, a bacterium is capable of releasing an antioxidant our body produces endogenously to enhance its proliferation. This information is not necessarily useful but quite interesting and gives you an idea of the *programmed* or *active* intelligence of bacterium.

"<>Macrophages are critical mediators of innate immunity and must be overcome for bacterial pathogens to cause disease. The Gram-positive bacterium Staphylococcus aureus produces virulence factors that impede macrophages and other immune cells. We previously determined that production of the metabolic cofactor lipoic acid by the lipoic acid synthetase, LipA, blunts macrophage activation. A ΔlipA mutant was attenuated during infection and was more readily cleared from the host. We hypothesized that bacterial lipoic acid synthesis perturbs macrophage antimicrobial functions and therefore hinders the clearance of S. aureus.
<>Here, we found that enhanced innate immune cell activation after infection with a ΔlipA mutant was central to attenuation in vivo, whereas a growth defect imparted by the lipA mutation made a negligible contribution to overall clearance. Macrophages recruited to the site of infection with the ΔlipA mutant produced larger amounts of bactericidal reactive oxygen species (ROS) and reactive nitrogen species (RNS) than those recruited to the site of infection with the wild-type strain or the mutant strain complemented with lipA. ROS derived from the NADPH phagocyte oxidase complex and RNS derived from the inducible nitric oxide synthetase, but not mitochondrial ROS, were critical for the restriction of bacterial growth under these conditions. Despite enhanced antimicrobial immunity upon primary infection with the ΔlipA mutant, we found that the host failed to mount an improved recall response to secondary infection.

<>Our data suggest that lipoic acid synthesis in S. aureus promotes bacterial persistence during infection through limitation of ROS and RNS generation by macrophages. Broadly, this work furthers our understanding of the intersections between bacterial metabolism and immune responses to infection."[450]

Quercetin & Ascorbic Acid are potent AGE Inhibitors

Quercetin, being arguably the most potent phytochemical antioxidant compound, and Ascorbic Acid (Vitamin-C), being an extremely common and inexpensive essential nutrient and antioxidant, both inhibit AGE formation.

"<>In the examined concentrations quercetin showed the greatest degree of inhibition for T-AGE (60.5 %) as well as for HMW-AGE (79.5 %), while in the case of LMW-AGE the greatest degree of glycation inhibition was shown by Padma Circosan (74.9 %). T-AOPP and HMW-AOPP were best inhibited by vitamin C (87.3 and 89.1 % respectively). The results obtained for LMW-AOPP are atypical, but the lowest concentration was observed in a sample with Padma 28."[451]

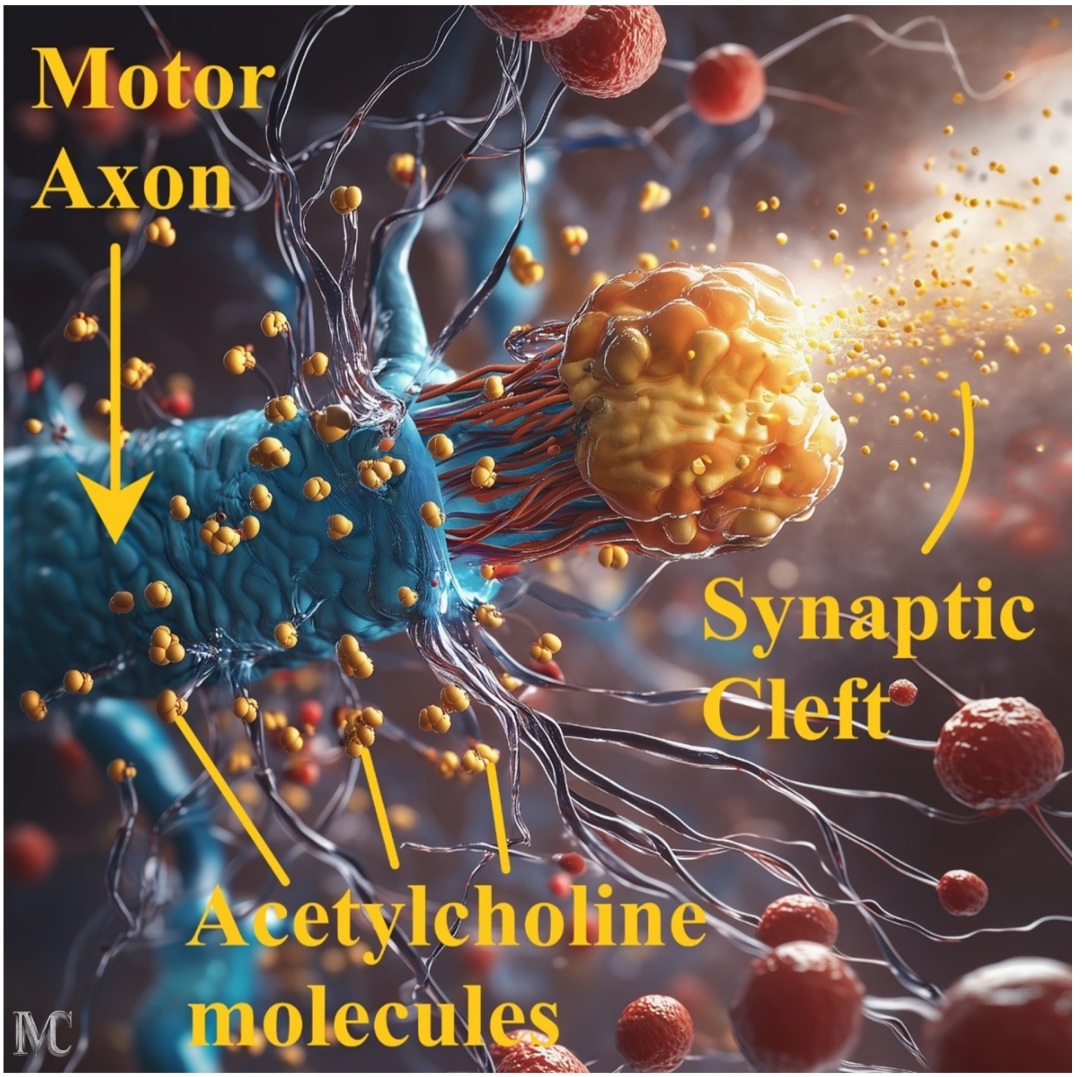
Motor Units, Muscle Contraction, & Neuromuscular Junctions

Motor Units

A Motor Unit is a motor neuron that innervates a bundle of skeletal muscle fibers, often one motor unit *controls* thousands of muscle fibers. A motor neuron is simply a motor axon that hovers over a motor endplate which is situated upon a muscle fiber bundle. Before muscle contraction the brain produces action potentials, which travel down the brainstem to the spine, to skeletal muscle motor axons. The motor axons are activated and thereby release Acetylcholine molecules from their synaptic vesicles which flow between a tiny gap called the Synaptic Cleft, this is where the synapses are located. The Acetylcholine molecules bind to the nAChRs situated upon the surface of the muscle fibers and stimulate a cascade of chemical reactions that cause electrical changes (ion changes) within a muscle, which results in the creation of a *second* action potential, and muscle contraction.

For a more accurate explanation of muscle contraction:

Neuronal Action Potential > Ach Release >
nAChR Channel opening > Muscle Membrane Na+ Ion Influx >
Na+ Threshold Maxing (First Depolarization) > Muscular Action Potential Generation >
T-Tubule Na+ Ions Influx >
Na+ Threshold Maxing (Second Depolarization) > Ca2+ Release >
Activation of the Troponin-Tropomyosin conformation change (muscle contraction).



Motor Units do not experience fatigue directly, but by proxy of the Central Nervous System, which fatigues rapidly during high intensity exercise. Interestingly, Motor Units may show "signs of fatigue" due to exercise-induced neurotransmitter changes, such as the Serotonin increases and Dopamine decreases that accompany strenuous exercise, leading to neurological exhaustion occurring during and post-exercise. Aerobic exercise appears to enhance dopamine levels, whereas strenuous or prolonged higher intensity forms of exercise decrease dopamine levels in the brain, thus strengthening the argument to engage in warmups pre-workout, including extended aerobics (walking, cycling, hiking, etc.).

"<>Aerobic exercise has been shown to increase dopamine levels in the striatum, hypothalamus, midbrain, and brainstem in various animal studies (Foley and Fleshner, 2008), further supporting the beneficial effects of exercise on memory and mood. <>Increases in serotonin and dopamine seem to modulate fatigue upon prolonged exercise. Exhaustion appears to set in when dopamine levels start to drop while serotonin levels are still elevated (Meeusen and De Meirleir, 1995). The serotonin agonist

quipazine dimaleate (acting on the 5-HT3 receptor) appears to shorten time to exhaustion and withholds the exercise-induced dopamine boost normally occurring after around 1 h of running in tested animals. The serotonin receptor antagonist LY53857 can increase time to exhaustion and prevents the dopamine decrease (Meeusen and De Meirleir, 1995). This fact may explain why runners usually take food supplements based on tyrosine, the precursor of dopamine, during endurance training, given that it could prevent the decrease of dopamine. Not surprisingly, several studies have shown that the intake of tyrosine may compensate cognitive decline associated with cognitive challenges (Colzato et al., 2014; Steenbergen et al., 2015) and stress (Deijen and Orbleke, 1994)."[451.0]

Neuromuscular Junctions

The Neuromuscular Junction can grow depending on training, primarily through enhanced synaptic plasticity (an increase in synapse number or to synapse strength) just as with neurons. As we age, we tend to lose our motor neurons.
The Mind-Muscle connection is not pseudoscience; it is a term to explain the conscious development and control over our myofibers through enhancing neuromuscular junction growth and motor memory strength.

[A] The Neuromuscular Junction grows in response to resistance training.

"The aim of this study was to determine the impact of resistance exercise on neuromuscular junction (NMJ) architecture. Eighteen Sprague-Dawley rats either participated in a 7-week resistance training program or served as untrained controls. Following the experimental period, the NMJs of soleus muscles were visualized with immunofluorescent techniques, and muscle fibers were stained histochemically. Results indicate that resistance training significantly ($P < 0.05$) increased endplate perimeter length (15%) and area (16%), and significantly enhanced the dispersion of acetylcholine receptors within the endplate region. Pre- and post-synaptic modifications to resistance exercise were well-coupled. No significant alterations in muscle fiber size or fiber type were detected. The data presented here indicate that the stimulus of resistance training was sufficiently potent to remodel NMJ structure, and that this effect cannot be attributed to muscle fiber hypertrophy or fiber type conversion."[451.1]

[B] The Central Nervous System (Spinal Cord) controls muscle force output.
"<>The strength of a muscle typically begins to increase after only a few sessions of strength training. This increase is usually attributed to changes in the neural drive to muscle as a result of adaptations at the cortical or spinal level. We investigated the change in the discharge characteristics of large populations of longitudinally tracked motor units in tibialis anterior before and after 4 weeks of strength training the ankle-dorsiflexor muscles with isometric contractions. The adaptations exhibited by 14 individuals were compared with 14 control subjects.
<>High-density electromyogram grids with 128 electrodes recorded the myoelectric activity during isometric ramp contractions to the target forces of 35%, 50% and 70% of

maximal voluntary force. The motor unit recruitment and derecruitment thresholds, discharge rate, interspike intervals and estimates of synaptic inputs to motor neurons were assessed. The normalized recruitment-threshold forces of the motor units were decreased after strength training ($P < 0.05$). Moreover, discharge rate increased by 3.3 ± 2.5 pps (average across subjects and motor units) during the plateau phase of the submaximal isometric contractions ($P < 0.001$). Discharge rates at recruitment and derecruitment were not modified by training ($P < 0.05$). The association between force and motor unit discharge rate during the ramp-phase of the contractions was also not altered by training ($P < 0.05$).
<>These results demonstrate for the first time that the increase in muscle force after 4 weeks of strength training is the result of an increase in motor neuron output from the spinal cord to the muscle."[452.0]

[B2] Alpha-motor neurons originate from the brainstem and spinal cord and innervate muscle fibers.

"<>Alpha-motor neurons form endings designed to deliver stimuli to extrafusal muscle fibres, and similar but smaller endings are formed by γ-motor neurons on intrafusal fibres. The junction between a motor neuron and a muscle cell involves elaboration of both the neuron and the muscle cell and of certain surrounding tissues, the entire complex being known as a motor endplate.
<>The terminal expansion of the motor neuron contains vesicles filled with the transmitter substance acetylcholine. When an action potential arrives at the nerve terminal, the vesicles release the acetylcholine through the presynaptic membrane into the synaptic deft. The transmitter substance then flows across the cleft to react with molecular receptors on the postjunctional membrane which generates an action potential in the muscle membrane. This potential is then propagated into the muscle cell to cause contraction of the muscle fibres."[452]

[C] Muscle contraction requires calcium ions and the sarcolemma to generate action potentials.

"<>All living cells have membrane potentials, or electrical gradients across their membranes. The inside of the membrane is usually around -60 to -90 mV, relative to the outside. This is referred to as a cell's membrane potential. Neurons and muscle cells can use their membrane potentials to generate electrical signals. They do this by controlling the movement of charged particles, called ions, across their membranes to create electrical currents. This is achieved by opening and closing specialized proteins in the membrane called ion channels. Although the currents generated by ions moving through these channel proteins are very small, they form the basis of both neural signaling and muscle contraction. Both neurons and skeletal muscle cells are electrically excitable, meaning that they are able to generate action potentials. An action potential is a special type of electrical signal that can travel along a cell membrane as a wave. This allows a signal to be transmitted quickly and faithfully over long distances.

<>Although the term excitation-contraction coupling confuses or scares some students, it comes down to this: for a skeletal muscle fiber to contract, its membrane must first be "excited"—in other words, it must be stimulated to fire an action potential. The muscle fiber action potential, which sweeps along the sarcolemma as a wave, is "coupled" to the actual contraction through the release of calcium ions (Ca++) from the SR. Once released, the Ca++ interacts with the shielding proteins, forcing them to move aside so that the actin-binding sites are available for attachment by myosin heads. The myosin then pulls the actin filaments toward the center, shortening the muscle fiber."[453]

[D] As a reminder, muscle hypertrophy does not relate to muscle force output. It is always wise to decide before you enter the gym, is your goal Size (1), Strength (2), or Power (3)? That equates to High Volume Low-Moderate Load Training (1), High Volume-High Load Training (2), and Low Volume-High Load Training (3). To attempt to build muscle force to the maximal extent alongside hypertrophy is very illogical as you will overtrain i.e. *damage-your-muscles-beyond-their-ability-to-adapt*.

"<>The increase in strength following exercise is typically in proportion to the specificity of the skill and specificity of the load. The greatest change in strength occurs in the movement trained and those training heavier tend to be better at lifting heavier than those who have been training with a lighter load. We hypothesize that these changes in strength may be due to changes within the nervous system and changes at the fiber level that occur independently of changes in muscle size. For example, a recent meta-analysis on fiber-level changes concluded that neural adaptations and mechanisms intrinsic to the fiber itself (independent of growth) may explain the change in strength following exercise. Neural adaptations could be occurring in the primary motor cortex, spinal cord, and/or via alterations in the alpha motor neuron. Changes intrinsic to the fiber may include a change in the composition of the myosin motors, changes in the pattern of calcium release, and/or changes in the major components of the excitation contraction coupling process."[453.1]

[E] Acetylcholine is the most important factor controlling muscle contraction.

[E2] "<>Acetylcholine, often abbreviated as ACh, is a neurotransmitter released by motor neurons that binds to receptors in the motor end-plate. It is an extremely important small molecule in human physiology. On the neuron side of the synaptic cleft, there are typically 300,000 vesicles waiting to be exocytosed at any time and each vesicle contains up to 10,000 molecules of acetylcholine."[454]

[E3] "<>ACh is produced by the reaction of Acetyl coenzyme A (CoA) with a choline molecule in the neuron cell body. After it is packaged, transported, and released, it binds to the acetylcholine receptor on the motor end-plate; it is degraded in the synaptic cleft by the enzyme acetylcholinesterase (AChE) into acetate (and acetic acid) and choline. The choline is recycled back into the neuron. AChE resides in the synaptic cleft, breaking down ACh so that it does not remain bound to ACh receptors, which would interrupt

normal control of muscle contraction. In some cases, insufficient amounts of ACh prevent normal muscle contraction and cause muscle weakness."[455]

[F] Grunting enhances muscle force output, and this is clearly due to a rapid (millisecond) stimulation of the fight-or-flight response, which would result in an immediate hysteria-like rise in cortical excitation, and greater resultant action potential generation & frequency, leading to enhanced force output.

"<>The aim of this study was to examine the effects of grunting on velocity and force production during dynamic and static tennis strokes in collegiate tennis players. Thirty-two (16 male and 16 female) division II and III collegiate tennis athletes with a mean age of 20.2 ± 1.89 years participated as subjects. Demographic and survey data were obtained before subjects completed a 10- to 15-minute warm-up of serves and ground strokes while grunting and not grunting.
<>The subjects performed randomized sets (3 grunting and 3 nongrunting trials) of serves and forehand strokes both dynamically and isometrically. Stroke velocities and isometric forces were measured with a calibrated radar gun and calibrated dynamometer, respectively. Electromyographic (EMG) data from subjects' dominant pectoralis major and contralateral external oblique muscles were recorded and averaged for data analysis. A repeated measures multivariate analysis of variance (RM-MANOVA) compared dynamic stroke velocity, isometric muscle force, and peak EMG activity during each breathing condition at the 0.05 alpha level. The RM-MANOVA indicated that dynamic velocity and isometric force of both serves and forehand strokes were significantly greater when the subjects grunted ($F = 46.572$, $p < 0.001$, power = 1.00). Peak muscle activity in the external oblique and pectoralis major muscles was also greater when grunting during both types of strokes ($F = 3.867$, $p = 0.05$, power = 0.950). Grunt history, gender, perceived advantages, and disadvantages of grunting, years of experience, highest level of competition, and order of testing did not significantly alter any of these results.
<>The velocity, force, and peak muscle activity during tennis serves and forehand strokes are significantly enhanced when athletes are allowed to grunt."[455.1]

Neuromuscular Junction Supplementation & Modalities

[A] Alpha-GPC is the most valuable supplement for athletes, as it is essential for muscle contraction, and research is beginning to display its potential as an ergogenic.

"<>Ergogenic aides are widely used by fitness enthusiasts and athletes to increase performance. Alpha glycerylphosphorylcholine (A-GPC) has demonstrated some initial promise in changing explosive performance. The purpose of the present investigation was to determine if 6 days of supplementation with A-GPC would augment isometric force production compared to a placebo.
<>Thirteen college-aged males gave written informed consent to participate in the study. The study was a double blind, placebo controlled, cross-over design. The participants reported to the lab for an initial visit where they were familiarized with the isometric mid

thigh pull in a custom squat cage on a force platform and upper body isometric test against a high frequency load cell, and baseline measurements were taken for both. The participant then consumed either 600 mg per day of A-GPC or placebo and at the end of 6 days performed isometric mid thigh pulls and an upper body isometric test. A one-week washout period was used before the participants' baseline was re-measured and crossed over to the other treatment.
<>Results: The A-GPC treatment resulted in significantly greater isometric mid thigh pull peak force change from baseline ($t = 1.76$, $p = 0.044$) compared with placebo (A-GPC: 98.8. ± 236.9 N vs Placebo: −39.0 ± 170.9 N). For the upper body test the A-GPC treatment trended towards greater change from baseline force production (A-GPC: 50.9 ± 167.2 N Placebo: −14.9 ± 114.9 N) but failed to obtain statistical significance ($t = 1.16$, $p = 0.127$).
<>Conclusions: A-GPC is effective at increasing lower body force production after 6 days of supplementation. Sport performance coaches can consider adding A-GPC to the diet of speed and power athletes to enhance muscle performance."[456]

[A2] Alpha-GPC by way of activation of nAChRs prevents muscle disuse atrophy making this a hidden gem to be included in both cycles, especially if you dislike Nicotine.

"<>Denervation of skeletal muscles induces severe muscle atrophy, which is preceded by cellular alterations such as increased plasma membrane permeability, reduced resting membrane potential and accelerated protein catabolism. The factors that induce these changes remain unknown. Conversely, functional recovery following denervation depends on successful reinnervation.
<>Here, we show that activation of nicotinic acetylcholine receptors (nAChRs) by quantal release of acetylcholine (ACh) from motoneurons is sufficient to prevent changes induced by denervation. Using in vitro assays, ACh and non-hydrolysable ACh analogs repressed the expression of connexin43 and connexin45 hemichannels, which promote muscle atrophy. In co-culture studies, connexin43/45 hemichannel knockout or knockdown increased innervation of muscle fibers by dorsal root ganglion neurons. Our results show that ACh released by motoneurons exerts a hitherto unknown function independent of myofiber contraction. nAChRs and connexin hemichannels are potential molecular targets for therapeutic intervention in a variety of pathological conditions with reduced synaptic neuromuscular transmission."[456.1]

[A3] Acetylcholine is secreted from Adipose Tissue, which thereby promotes myogenesis, thus explaining another mechanism through which increased adiposity can promote muscle growth, and further validating the use of Alpha-GPC in athletes.

"<>Introduction: In this study we investigated the interaction between adipose tissue-derived stem cells (ASCs) and myoblasts in co-culture experiments.
>Methods: Specific inductive media were used to differentiate ASCs in vitro into a Schwann cell-like phenotype (differentiated adipose tissue-derived stem cells, or dASCs)

and, subsequently, the expression of acetylcholine (ACh)-related machinery was determined. In addition, the expression of muscarinic ACh receptors was examined in denervated rat gastrocnemius muscles.
<>Results: In contrast to undifferentiated ASCs, dASCs expressed more choline acetyltransferase and vesicular acetylcholine transporter. When co-cultured with myoblasts, dASCs enhanced the proliferation rate, as did ACh administration alone. Western blotting and pharmacological inhibitor studies showed that phosphorylated extracellular signal-regulated kinase 1/2 signaling mediated these effects. In addition, denervated muscle showed higher expression of muscarinic ACh receptors than control muscle.
<>Discussion: Our findings suggest that dASCs promote proliferation of myoblasts through paracrine secretion of ACh, which could explain some of their regenerative capacity in vivo."[456.2]

[B] Black Tea Theaflavins activate the neuromuscular junction.

"<>The effect of various fractions of black tea (Camellia Sinensis) on the function of mammalian skeletomotor apparatus was studied. The theaflavin fraction (Tfs) produced a concentration- dependent facilitation of indirect twitch responses of the rat phrenic nerve diaphragm preparation and the facilitation was dependent on the amount of calcium present in the bathing fluid. Nifedipine reduced the facilitatory effect of Tfs as a function of its concentration. Tfs failed to produce facilitation when the twitch height was reduced to about 50% of the control value in presence of magnesium chloride. Tfs completely antagonized the submaximal paralytic effect of d- tubocurarine and decamethonium bromide. Tfs did not have any effect on direct twitch responses or on acetylcholine (Ach) and potassium chloride (KCl) induced contractures of denervated diaphragm.
<>The results revealed that the site of action of Tfs is on the contractile mechanism of the voluntary muscle and point to a critical role of calcium in the mechanism of action of Tfs. N omega-nitro-L-arginine-methyl ester (L-NAME), a nitric oxide synthase (NOS) inhibitor, antagonized both the facilitatory and inhibitory effects on indirect twitch responses of rat diaphragm induced by L-arginine and Tfs when the phrenic nerve was stimulated at 5 Hz and 50 Hz respectively. The thearubigin (Trs) fraction of black tea and the aqueous part which is completely devoid of Tfs, did not potentiate the twitch responses.
<>The findings suggest that Tfs have a potentiating effect on the contractile mechanism of skeletal muscle and that calcium and nitric oxide may modulate this action of Tfs."[457]

[C] Carnosine enhances muscle contraction but not force, this means Beta-Alanine will promote strength-endurance gains. [See: Anti-Inflammation Cycle Supplementation: Beta-Alanine]

"<>The effect of dipeptides (carnosine and anserine) on a neuromuscular preparation under fatigue or diplacine blocking is shown to result in a significant restoration of the

muscle contraction. The analysis of this phenomenon evidences that synaptic processes are not responsible for the restoration, at least under the given experimental conditions. At the same time, the absence of any effect of the compounds studied on the maximal rate of isotonic shortening and on the tension of glycerinized fibres and ATPPase of native and desenitized actomyosine indicates that the contractile mechanism is not involved in the effect described. On the other hand, the dipeptides restore the value of the transmembrane potential depolarized by exhaustion, increase the amplitude of isometric twitch and the value of maximal load under isotonic conditions. Moreover, the time of the contractile cycle in the presence of the dipeptides is considcted to the processes of electromechanical coupling in skeletal muscles."[457.1]

[D] DHA promotes improved reaction time, not neuromuscular junction performance, but a healthier motor cortex will certainly benefit athletes.

"<>Omega-3 fatty acids (n-3) has shown to improve neuromotor function. This study examined the effects of docosahexaenoic acid (DHA) on complex reaction time, precision and efficiency, in female elite soccer players. 24 players from two Spanish female soccer Super League teams were randomly selected and assigned to two experimental groups, then administered, in a double-blind manner, 3.5 g·day(-1) of either DHA-rich fish oil (FO =12) or olive oil (OO = 12) over 4 weeks of training. Two measurements (pre- and post-treatment) of complex reaction time and precision were taken. Participants had to press different buttons and pedals with left and right hands and feet, or stop responding, according to visual and auditory stimuli. Multivariate analysis of variance displayed an interaction between supplement administration (pre/post) and experimental group (FO/OO) on complex reaction time (FO pre = 0.713 ± 0.142 ms, FO post = 0.623 ± 0.109 ms, OO pre = 0.682 ± 1.132 ms, OO post = 0.715 ± 0.159 ms; p = 0.004) and efficiency (FO pre = 40.88 ± 17.41, FO post = 57.12 ± 11.05, OO pre = 49.52 ± 14.63, OO post = 49. 50 ± 11.01; p = 0.003).
<>It was concluded that after 4 weeks of supplementation with FO, there was a significant improvement in the neuromotor function of female elite soccer players. Key points. The results obtained from the study suggest that supplementation with DHA produced perceptual-motor benefits in female elite athletes. DHA could be a beneficial supplement in sports where decision making, and reaction time efficiency are of importance."[458]

[E] Dopamine receptors protect muscles from atrophy and force loss. Explaining the impressive physical strength "Crack Heads" possess, and explaining the reasoning behind a famous 1981 era strongman—whose name I will not mention—admitting to experimenting with amphetamines during competition.
"<>Control of muscle mass and force production is a complex physiological process involving numerous regulatory systems. Agents that increase skeletal muscle cAMP levels have been shown to modulate skeletal muscle mass and force production. The dopamine 1 receptor and its closely related homolog, the dopamine 5 receptor, are G-protein coupled receptors that are expressed in skeletal muscle and increase cAMP levels

when activated. Thus, we hypothesize that activation of the dopamine 1 and/or 5 receptor will increase skeletal muscle cAMP levels thereby modulating skeletal muscle mass and force production.
<>We treated isolated mouse tibialis anterior (TA) and medial gastrocnemius (MG) muscles in tissue bath with the selective dopamine 1 receptor and dopamine 5 receptor agonist SKF 81297 to determine if activation of skeletal muscle dopamine 1 and dopamine 5 receptors will increase cAMP. We dosed wild-type mice, dopamine 1 receptor knockout mice and dopamine 5 receptor knockout mice undergoing casting-induced disuse atrophy with SKF 81297 to determine if activation of the dopamine 1 and dopamine 5 receptors results in hypertrophy of non-atrophying skeletal muscle and preservation of atrophying skeletal muscle mass and force production.
<>Results: In tissue bath, isolated mouse TA and MG muscles responded to SKF 81297 treatment with increased cAMP levels. Treating wild-type mice with SKF 81297 reduced casting-induced TA and MG muscle mass loss in addition to increasing the mass of non-atrophying TA and MG muscles. In dopamine 1 receptor knockout mice, extensor digitorum longus (EDL) and soleus muscle mass and force was not preserved during casting with SKF 81297 treatment, in contrast to significant preservation of casted wild-type mouse EDL and soleus mass and EDL force with SKF 81297 treatment. Dosing dopamine 5 receptor knockout mice with SKF 81297 did not significantly preserve EDL and soleus muscle mass and force although wild-type mouse EDL mass and force was significantly preserved SKF 81297 treatment.
<>Conclusions: These data demonstrate for the first time that treatment with a dopamine 1/5 receptor agonist results in (1) significant preservation of EDL, TA, MG and soleus muscle mass and EDL muscle force production during periods of atrophy and (2) hypertrophy of TA and MG muscle. These effects appear to be mainly mediated by both the dopamine 1 and dopamine 5 receptors."[459]

[F] Norepinephrine is important for muscle force generation.

"<>Recruitment and repetitive firing of spinal motoneurons depend on the activation of persistent inward calcium and sodium currents (PICs) that are in turn facilitated by serotonin and norepinephrine that arise primarily from the brain stem. Considering that in rats motoneuron PICs are greatly facilitated by increasing the presynaptic release of norepinephrine with amphetamine, we sought similar evidence for the modulation of PICs in human motoneurons. Pairs of motor units were recorded during a gradually increasing and then decreasing voluntary contraction. The firing frequency (F) of the lower-threshold (control) motor unit was used as an estimate of the synaptic input to the higher-threshold (test) motor unit.
<>Generally, PICs are initiated during the recruitment of a motoneuron and subsequently provide a fixed depolarizing current that helps the synaptic input maintain firing until derecruitment. Thus the amplitude of the PIC in the test motor unit was estimated from the difference in synaptic input (DeltaF) needed to maintain minimal firing once the PIC was fully activated (measured at the time of test unit derecruitment) compared with the

larger synaptic input required to initiate firing prior to full PIC activation (measured at the time of test unit recruitment; DeltaF = F(recruit) - F(derecruit)).
<>Moreover, the activation time of the PIC was estimated as the minimal contraction duration needed to produce a maximal PIC (DeltaF). In five subjects, oral administration of amphetamine, but not placebo, increased the DeltaF by 62% [from 3.7 +/- 0.6 to 6.0 +/- 0.8 (SD) imp/s, P = 0.001] and decreased the time needed to activate a maximal DeltaF from approximately 2 to 0.5 s. Both findings suggest that the endogenous facilitation of PICs from brain stem derived norepinephrine plays an important role in modulating human motoneuron excitability, readying motoneurons for rapid and sustained activity during periods of high arousal such as stress or fear."[460]

[G] HIT enhances neuromuscular junction growth. Although let me clarify again… HIT / HIIT for test animals equates to high volume, low load, explosive movements such as running, not low volume-high load explosive strength training. That is not to say speedwork is ineffective, but explosive strength is dangerous to tendon integrity and does not align with animal studies. It is not a coincidence that Eddie Hall used to be an Olympic Swimmer which involved explosive, high volume, low load, & high intensity exercise prior to becoming a powerlifter.

"<>Little is known about the effects of exercise training on neuromuscular junction morphology in skeletal muscle. The objectives of this investigation were: 1) to determine if exercise training would elicit changes in neuromuscular junction morphology, 2) to determine if exercise training of different intensities would evoke specific changes in neuromuscular junction morphology, and 3) to determine whether changes in neuromuscular junction structure occur independently of changes in muscle fibre type and size. Twenty-four age and size matched male Sprague-Dawley rats were randomly assigned to three groups: high-intensity trained (HIT), low-intensity trained (LIT), or untrained.
<>Neuromuscular junction morphology of the soleus muscle was determined via immunofluorescent staining. Presynaptic acetylcholine vesicles were visualized with SV-2 antibody in conjunction with fluorescein isothiocyanate labelled secondary secondary antibody. Postsynaptic acetylcholine receptors were identified with rhodamine labelled alpha-bungarotoxin. Laser scanning microscopy was used to produce images of synapses, which were used to quantitate the following: total area of SV-2 and alpha-bungarotoxin staining, density of acetylcholine vesicles and receptors, structural complexity, and synaptic coupling.
<>To visualize nerve terminal branching, a smaller number of neuromuscular junctions were stained with C-2 antibody, which reacts with a neurofilament epitope, in conjunction with fluorescein isothiocyanate labelled secondary antibody. Total length of branching, number of branches, average length of branches, and ratio of secondary to primary branches per neuromuscular junction were determined. Citrate synthase activity, fibre type composition and fibre cross-sectional areas of the soleus muscle were assessed to determine the presence of a training effect in that muscle. Results indicate that training

did induce hypertrophy of the neuromuscular junction that was independent of muscle hypertrophy.
<>Although the HIT and LIT groups exhibited similar hypertrophic responses of the neuromuscular junction, the HIT group displayed more dispersed synapses than the LIT group. Neither exercise training program, however, resulted in altered densities of acetylcholine vesicles or receptors, nor did training significantly change synaptic coupling. Nerve terminal branching was also affected by exercise training. Neuromuscular junctions from the HIT group demonstrated a greater total length of branching, average length per branch, and number of finer, or secondary, branches than those of the LIT group."[461]

[H] Mental Imagery enhances muscle strength.

"<>The aims of the present review were to (i) provide a critical overview of the current literature on the effects of mental imagery on muscular strength in healthy participants and patients with immobilization of the upper extremity (i.e., hand) and anterior cruciate ligament (ACL), (ii) identify potential moderators and mediators of the "mental imagery-strength performance" relationship and (iii) determine the relative contribution of electromyography (EMG) and brain activities, neural and physiological adaptations in the mental imagery-strength performance relationship. <>This paper also discusses the theoretical and practical implications of the contemporary literature and suggests possible directions for future research. Overall, the results reveal that the combination of mental imagery and physical practice is more efficient than, or at least comparable to, physical execution with respect to strength performance. Imagery prevention intervention was also effective in reducing of strength loss after short-term muscle immobilization and ACL.
<>The present review also indicates advantageous effects of internal imagery (range from 2.6 to 136.3%) for strength performance compared with external imagery (range from 4.8 to 23.2%). Typically, mental imagery with muscular activity was higher in active than passive muscles, and imagining "lifting a heavy object" resulted in more EMG activity compared with imagining "lifting a lighter object".
<>Thus, in samples of students, novices, or youth male and female athletes, internal mental imagery has a greater effect on muscle strength than external mental imagery does. Imagery ability, motivation, and self-efficacy have been shown to be the variables mediating the effect of mental imagery on strength performance. Finally, the greater effects of internal imagery than those of external imagery could be explained in terms of neural adaptations, stronger brain activation, higher muscle excitation, greater somatic and sensorimotor activation and physiological responses such as blood pressure, heart rate, and respiration rate."[462]

TALMS

Regarding what I believe will be the future of Myogenic & Weight Loss Therapy; I coin a term called **Topically Applied Lipolytic-Myogenic chemical © (TALM)**. The most

potent and widely available TALM's will be made from combing Essential oils (EO), which are basically super concentrated liquid herbal extracts.

My favorite three EO's I have found are Eucalyptus Globulus oil, Sandalwood oil, & Peppermint oil, but I suggest you continue to research Essential oil chemical components as this field of study is still in its infancy.

It is important to understand that Camphor is proconvulsant, selfsame as Eucalyptol (Cineole), one must use caution to use very little of these compounds by diluting them with a carrier oil. I would suggest never exceeding 2-Tablespoon (Two for those who are ill) of Eucalyptus Globulus oil and 2/4th Teaspoon of Camphor oil applied to skin per day, for no longer than a few weeks before a week washout period. I also suggest cycling off TALM's for one week every five or six weeks of concurrent daily use to avoid damaging the integumentary system.

The carrier oil is the diluter and should be close to 50-80% of the TALM mixture, depending on tolerance, careful self-experimentation will be required as I will not venture to suggest exact dosing percentages. Kiwi Seed oil is high in Alpha Linolenic acid has a very low viscosity and is ideal for fast absorption, whereas Grapeseed oil, having a high Linoleic acid content, is better for longer application periods. Sunflower oil is an unmentioned third carrier oil to use, but its odor may dissuade people from its use. Ensure you only purchase organic or solvent-free oils to use as carrier oils.

Many Essential oils contain cytotoxic chemical constituents, some of which are phototoxic (magnifying UV-induced skin damage) such as Citrus oils & Bergamot oil. Use caution and engage in careful research before applying any Essential oil to your skin[462.0]. Do be careful not to conflate Volatile Organic Compound (VOC) cancer or tumor cell line cytotoxicity in research articles with healthy cell line cytotoxicity, nearly every phytochemical will display cytotoxic activity against aberrant cell lines, an example is the A431 (cancer) cell line vs the HaCaT (healthy) cell line.

Finally, because VOC's are extremely powerful chemicals and may damage the skin, eyes, or other body parts, you should consult with a dermatologist or other medical professional before applying any Essential oil to your skin.

TALM V1 (Myogenesis / Lipolysis):

In order of high>low ratio percentages:

- Week 1: AM Camphor oil & Grapeseed Seed or Kiwi Seed oil as the diluter applied to regenerating muscles.
  PM Eucalyptus oil & Grapeseed Seed or Kiwi Seed oil as the diluter applied to regenerating muscles.
- Week 2: Peppermint oil with a *smaller amount* (20-40%) of Grapeseed or Kiwi Seed oil as the diluter applied to regenerating muscles or small areas of fat. Note: Because Peppermint oil (menthol) poses little toxicity when applied topically, you may use a large amount on your skin per day, but low concentrations do enter into the bloodstream and will affect mood and memory, pay close attention to your mood after application to find a comfortable dosage.

TALM V2 (Collagen Synthesis):

In order of high>low ratio percentages:

- Week 1: Carrot Seed oil + Adapalene Gel & Grapeseed Seed or Kiwi Seed oil as the diluter applied to the facial skin. [See: The Skin: Adapalene]
- Week 2: Carrot Seed oil + Lavender Latifolia oil & Grapeseed Seed or Kiwi Seed oil as the diluter applied to the facial skin.

TALM V3 (Joint Health)

In order of high>low ratio percentages:
Ginger oil + Juniper Berry oil + Black Pepper oil + Nutmeg oil + Clove oil + Rosemary oil + Bitter orange oil + Lavender Angustifolia oil + Pine Needle oil + Eucalyptus Globulus oil & Grapeseed Seed or Kiwi Seed oil as the diluter. Massage 1-2tsp into inflamed joints with surgical gloves twice per day.

TALM V4 (Anxiolytic)

In order of high>low ratio percentages:
East Indian Sandalwood oil + Juniper Berry oil & Kiwi Seed oil (necessary for quick absorption) as the diluter. Massage into feet (for its high number of blood vessels).

[A] A mixture of essential oils halts arthritis, See TALM V3 for a condensed version.

"<>This study was aimed at examining the effect of an ointment containing essential oils (EO) on the severity of adjuvant arthritis (AA), an experimental model of human rheumatoid arthritis (RA), in Lewis rats and to define the underlying mechanisms. At the onset of AA, rats received topical application twice daily of ointment containing 20% EO or placebo ointment. The synovial fluid (SF) and synovium-infiltrating cells (SIC) of rats were tested for pro-inflammatory cytokines TNF-α and IL-1β. The hind paws and skin were examined histologically. The activity/level of matrix metalloproteinases (MMPs) and anti-mycobacterial heat-shock protein 65 (Bhsp65) antibodies was tested. Arthritic rats treated with ointment containing EO developed less severe clinical arthritis compared to the controls, and this activity was attributable to EO and not the carrier oil. <>The levels of TNF-α and IL-1β, and the activity of MMPs in SF and SIC-lysate were significantly ($p<0.05$) reduced in EO-treated arthritic rats compared to the controls. However, the levels of anti-Bhsp65 antibodies were unaffected by treatment. Thus, topical dermal delivery of EO-containing ointment downmodulates the severity of AA in Lewis rats by inhibiting defined mediators of inflammation. Such ointments should be tested in patients with RA and other arthritic conditions."[462.1]

[B] Eucalyptol, Camphor, & Peppermint oils are skin penetration enhancers, making it necessary to add one or more of them to TALMs to ensure the chemical components of the primary Essential oils reach systemic circulation.

"<>In vivo skin microdialysis showed that camphor had a similar penetration behavior on transdermal absorption of model drugs. Meanwhile, the partition of lipophilic drugs into SC was increased after treatment with camphor, and camphor also produced a shift of CH2 vibration of SC lipid to higher wavenumbers and decreased the peak area of the CH2 vibration, probably resulting in the alteration of the skin permeability barrier. This suggests that camphor might be a safe and effective penetration enhancer for transdermal drug delivery."[466]

“<>Three essential oils as penetration enhancers for 5-fluorouracil (5-FU) were studied using excised rat skin. The oils used were eucalyptus, peppermint and turpentine. Azone was used for comparison. The enhancing effect of the oils was found to be less than that of azone, but all the oils used enhanced the permeation of 5-FU. Eucalyptus oil was found to be the most active, causing about 60 fold increase, while peppermint and turpentine caused 46 and 28 fold increase, respectively. Eucalyptus oil was further studied by grading it into 5 fractions according to difference in boiling points. It was found that their activities increased as their boiling point increased. With all enhancers increased partition coefficients were observed but the diffusion coefficient values obtained were comparatively higher. The mode of action of these accelerants may be described by combined processes of partition and diffusion, the diffusion process being dominant.”[466.1]

[B1] Camphor & Menthol enhance skeletal muscle blood flow. Although Camphor inhibits Menthols action on the TRPM8 receptors.

"<>Application of camphor to the skin has been empirically thought to improve blood circulation. However, camphor's effects on blood circulation to the skin and on thermal sensation have not been well elucidated. In this study, we examined its effects on the quality of sensation as well as on skin and muscle blood flow in human. Nine adults (average age 37±9.4 years) participated in the study. Petroleum jelly containing 5%, 10%, 20% camphor, or 2% menthol was separately applied to the skin on the medial side of one forearm of each subject. Just after the application, camphor at each concentration induced a cold sensation in a dose-dependent manner. Within 10 min, each subject reported that the cold sensation had faded, after which it was replaced by a warm sensation.
<>As reported previously, a cold sensation was induced by application of 2% menthol, but the subjects did not adapt to that sensation. In addition, menthol did not induce a warm sensation at all. Application of menthol has been shown to increase blood flow in the skin. Finally, we measured blood flow in skin and muscle after the application of camphor or menthol. Application of camphor or menthol separately induced increases in

local blood flow in the skin and muscle. The present results indicate that camphor induces both cold and warm sensations and improves blood circulation."[467]

[C] As an addendum: Olive oil damages the skin barrier. It's clearly a much better dressing than topical anti-aging or moisturizing agent.

"<>Natural oils are advocated and used throughout the world as part of neonatal skin care, but there is an absence of evidence to support this practice. The goal of the current study was to ascertain the effect of olive oil and sunflower seed oil on the biophysical properties of the skin. Nineteen adult volunteers with and without a history of atopic dermatitis were recruited into two randomized forearm-controlled mechanistic studies. The first cohort applied six drops of olive oil to one forearm twice daily for 5 weeks. The second cohort applied six drops of olive oil to one forearm and six drops of sunflower seed oil to the other twice daily for 4 weeks. The effect of the treatments was evaluated by determining stratum corneum integrity and cohesion, intercorneocyte cohesion, moisturization, skin-surface pH, and erythema. <>Topical application of olive oil for 4 weeks caused a significant reduction in stratum corneum integrity and induced mild erythema in volunteers with and without a history of atopic dermatitis. Sunflower seed oil preserved stratum corneum integrity, did not cause erythema, and improved hydration in the same volunteers. In contrast to sunflower seed oil, topical treatment with olive oil significantly damages the skin barrier, and therefore has the potential to promote the development of, and exacerbate existing, atopic dermatitis. The use of olive oil for the treatment of dry skin and infant massage should therefore be discouraged. These findings challenge the unfounded belief that all natural oils are beneficial for the skin and highlight the need for further research."[467.0]

East Indian (Santalum Album: *Not* Santalum Spicatum) Sandalwood Oil

Sandalwood oil is a very promising supplement / TALM that may enhance lifespan. Although the following study is on oral consumption, its chemical components do permeate into the skin and reach circulation [B], but it may activate Caspase-3 when applied topically, promoting skin aging [C]. At the very least inhalation of it will reach the brain and protect neuronal tissue, and application to the feet will result permeation into the blood. Only use East Indian (Santalum album) species of Sandalwood oil for its higher concentration of A / B-santalol.

[A] "<>East Indian Sandalwood Oil (EISO) has diverse beneficial effects and has been used for thousands of years in traditional folk-medicine for treatment of different human ailments. However, there has been no in-depth scientific investigation to decipher the neuroprotective and geroprotective mechanism of EISO and its principal components, α- and β-santalol. Hence the current study was undertaken to assess the protective effects of EISO, and α- and β-santalol against neurotoxic (6-OHDA/6-hydroxydopamine) and proteotoxic (α-synuclein) stresses in a Caenorhabditis elegans model. Initially, we found that EISO and its principle components exerted an excellent antioxidant and antiapoptotic

activity as it was able to extend the lifespan, and inhibit the ROS generation, and germline cell apoptosis in 6-OHDA-intoxicated C. elegans.
<>Further, we showed that supplementation of EISO, and α- and β-santalol reduced the 6-OHDA and α-synuclein-induced Parkinson's disease associated pathologies and improved the physiological functions. The genetic and reporter gene expression analysis revealed that an EISO, or α- and β-santalol-mediated protective effect does not appear to rely on DAF-2/DAF-16, but selectively regulates SKN-1 and its downstream targets involved in antioxidant defense and geroprotective processes. Together, our findings indicated that EISO and its principle components are worth exploring further as a candidate redox-based neuroprotectant for the prevention and management of age-related neurological disorders."[467.1]

[B] "The aim of the study was to investigate the effects of East Indian sandalwood oil (Santalum album, Santalaceae) and α-santalol on physiological parameters as well as on mental and emotional conditions in healthy human subjects after transdermal absorption. In order to exclude any olfactory stimulation, the inhalation of the fragrances was prevented by breathing masks. Eight physiological parameters, i. e., blood oxygen saturation, blood pressure, breathing rate, eye-blink rate, pulse rate, skin conductance, skin temperature, and surface electromyogram were recorded. Subjective mental and emotional condition was assessed by means of rating scales. While α-santalol caused significant physiological changes which are interpreted in terms of a relaxing/sedative effect, sandalwood oil provoked physiological deactivation but behavioral activation. These findings are likely to represent an uncoupling of physiological and behavioral arousal processes by sandalwood oil."[467.2]

[C] Sandalwood oil may or may not promote skin aging, depending on if it activates Caspase-3 in healthy skin. I suggest only applying it to the feet.

"<>This study is designed to investigate the chemopreventive effect and molecular mechanisms of α-santalol on UVB-induced skin tumor development in SKH-1 hairless mouse, a widely used model for human photocarcinogenesis. A dose of UVB radiation (30 mJ cm(-2) day(-1)) that is in the range of human sunlight exposure was used for the initiation and promotion of tumor.
<>Topical treatment of mice with α-santalol (10%, wt/vol in acetone) caused reduction in tumor incidence, multiplicity and volume. In our study, the anticarcinogenic action of α-santalol against UVB-induced photocarcinogenesis was found to be associated with inhibition of inflammation and epidermal cell proliferation, cell cycle arrest and induction of apoptosis. α-Santalol pretreatment strongly inhibited UVB-induced epidermal hyperplasia and thickness of the epidermis, expression of proliferation and inflammation markers proliferating cell nuclear antigen (PCNA), Ki-67 and cyclooxygenase 2 (Cox-2). Significant decrease in the expression of cyclins A, B1, D1 and D2 and cyclin-dependent kinases (Cdk)s Cdk1 (Cdc2), Cdk2, Cdk4 and Cdk6 and an upregulated expression of cyclin-dependent kinase (CDK) inhibitor Cip1/p21 were found in α-santalol pretreated group.

<>Furthermore, an elevated level of cleaved caspase 3 and cleaved poly (ADP-ribose) polymerase (PARP) were observed in α-santalol-treated group. Our data suggested that α-santalol is a safer and promising skin cancer chemopreventive agent with potential to target various pathways involved in photocarcinogenesis."[467.3]

[D] Australian Sandalwood oil (Santalum Spicatum) is not a good source of santalols. Instead use East Indian Sandalwood oil.

"<>West Australian sandalwood (Santalum spicatum) belongs to the genus of hemi-parasitic Santalum (Santalaceae) trees widely exploited for their fragrant heartwood which is used in perfumes, pharmaceuticals, incense and ornamental carvings. The fragrance contained in the heartwood of mature sandalwood trees (>10 years) consists of a complex mixture of sesquiterpenoids, with unique compositions apparent across, and often within species.
<>Historically, Indian sandalwood (S. album) has provided the bulk of sandalwood products; however, S. spicatum is frequently used as a supplement to incense feedstock and to a lesser extent as extracted fragrance oil.
<>The international standard for S. album oil requires 41%–55% of the sesquiterpene alcohol α-santalol and 16%–24% β-santalol. At present, S. spicatum extracts do not meet these industry standards for two reasons; the combined santalol content is too low, and levels of E,E-farnesol, a suspected allergen, are too high. Extracts of S. spicatum are generally considered less valuable than those of S. album due to the lower overall content and more variable sesquiterpene composition."[467.4]

Menthol

[A] Menthol appears to reduce muscle soreness.

"<>Influence of menthol on recovery from exercise-induced muscle damage. J Strength Cond Res 34(2): 451-462, 2020-This study assessed the influence of menthol, a cold receptor agonist, on recovery from exercise-induced muscle damage (EIMD). Forty-seven healthy males were allocated to a Control (CON, n = 18), Placebo (P, n = 14), or 4.0% Menthol (M, n = 15) condition. Participants were familiarized with a testing battery (TB) including perception of lower-body muscle soreness, hip flexion/abduction range of motion, vertical jump (VJ), and the agility T-test. Muscle damage was induced on day 1 using 40 × 15-m sprints with a 5-m deceleration zone. The TB immediately followed this and was repeated once-daily for 5 days. Over this time, participants in M and P applied gels to the lower body immediately after sprinting and twice-daily thereafter, whereas CON did nothing. Dependent variables were compared by condition using the Kruskal-Wallis test ($\alpha = 0.05$), and mean differences with 90% confidence intervals were calculated with small, moderate, and large effects.
<>A significant difference by condition ($p < 0.05$) in muscle soreness was found, and moderate to large effects were observed in the reduction of muscle soreness with P, compared with M or CON, indicating a placebo effect. A reduction in VJ height across

all conditions was observed, with a significant effect ($p < 0.05$) by condition, and moderate to large effects (1-5 cm) were observed in its preservation with menthol, compared with P or CON. No other differences were observed. These findings raise the possibility that menthol influences recovery of lower-body power after EIMD, and this may have practical implications for menthol's use when recovery of muscle power is important."[468]

[B] Large concentrations of Menthol, when applied to the entire body, promote lipolysis and mitigate adipogenesis through activating the Sympathetic Nervous System (SNS) and activating Brown Fat Thermogenesis (BAT).

"<>This study attempted to determine if, and how, topical MNTH application stimulates thermogenesis in physiologically humanized BAT of mice housed at thermoneutrality. Using multiple complimentary approaches to quantify thermogenesis in vivo, multiple models to quantify direct effects of MNTH ex vivo, and three different strains of mice, we were able to convincingly demonstrate the following: (1) acute topical MNTH application induces BAT thermogenesis in a TRPM8- and UCP1-dependent manner; (2) MNTH-induced BAT thermogenesis is sufficient to attenuate weight gain over time without affecting energy intake in both chow and high-fat diet-fed mice; (3) the ability of topical MNTH application to stimulate BAT thermogenesis is mediated, in part, by a central mechanism involving the release of norepinephrine.
<>These observations collectively support the generation of a working model whereby the topical application of MNTH to the skin activates TRPM8 to stimulate the afferent transmission of this signal to the SNS, the release of norepinephrine from catecholaminergic neurons innervating BAT, and the downstream activation of UCP1-dependent thermogenesis."[468.1]

[B2] The lipolytic effects of topical Menthol begin to attenuate after one week, consider therefore one week on / one week off during topical Menthol use.

"<>We then investigated which mechanisms would account for the attenuation in the menthol response. Although menthol-induced TRPM8 desensitization has been demonstrated in vitro, we ruled out this hypothesis. Animals treated with menthol are able to reach similar values of hyperthermic Tc even after repeated exposure to topical menthol, i.e., the attenuation in the menthol response is due to a shorter duration of the hyperthermia, suggesting that channels are not desensitized. Our results, as explained below, point to a shift in the thermoregulatory mechanisms recruited by the animals after repeated menthol, probably in an attempt to save energy. Because they started to recruit less energy-consuming but also less efficient thermoeffectors, they are not able to sustain the hyperthermic response as long as they do in response to acute treatment."[469]

[C] Camphor & Menthol have low transdermal absorption.

"<>Camphor, menthol, and methyl salicylate occur in numerous over-the-counter products. Although extensively used, there have been no estimates of human exposure following administration via dermal application. Furthermore, there is little information about the pharmacokinetics of those compounds. The authors report the plasma concentrations of the intact compounds as a function of dose following dermal patch application. Three groups of 8 subjects (4 male, 4 female) applied a different number of commercial patches (2, 4, or 8) to the skin for 8 hours. Plasma samples were assayed using sensitive and selective gas-chromatographic methods. For the 8-patch group, the average maximum plasma concentrations (Cmax +/- SD) were 41.0 +/- 5.8 ng/mL, 31.9 +/- 8.8 ng/mL, and 29.5 +/- 10.5 ng/mL for camphor, menthol, and methyl salicylate, respectively. The corresponding values for the 4-patch group were 26.8 +/- 7.2 ng/mL, 19.0 +/- 5.4 ng/mL, and 16.8 +/- 6.8 ng/mL. The harmonic mean terminal half-lives were 5.6 +/- 1.3 hours, 4.7 +/- 1.6 hours, and 3.0 +/- 1.2 hours for camphor, menthol, and methyl salicylate, respectively. The 2-patch group had measurable but low plasma concentrations of each compound.
<>Low-dose dermal application for an extended time results in low plasma concentrations of all 3 compounds. Four and 8 patches, when applied for 8 hours, gave measurable and nearly proportional plasma concentrations. Although unable to determine the absolute dermal bioavailability of these compounds, there appears to be relatively low systemic exposure to these potentially toxic compounds, even when an unrealistically large number of patches are applied for an unusually long time."[470]

[D] Oral Menthol in the dosages you'd need to use to burn fat are highly toxic, only use it through transdermal delivery.

"<>Pulegone and menthol, components of peppermint oil, were investigated in rats. The substances were administered by gavage for 28 days at 0, 20, 80, 160 mg pulegone and 0, 200, 400, 800 mg menthol/kg body wt./day, respectively. At the two highest doses, pulegone induced atonia, decreased blood creatinine content, lowered terminal body weight and caused histopathological changes in the liver and in the white matter of cerebellum. For menthol at all dose levels a significant increase in absolute and relative liver weights and vacuolisation of hepatocytes was found. No sign of encephalopathy was observed in rats given menthol. The no effect level for pulegone was 20 mg/kg body wt./day and for menthol less than 200 mg/kg body wt./day."[471]

Carrot Seed oil (Carotol)

This relatively unknown oil appears to be a great free radical scavenger.

"<>The present study deals with the evaluation of antiaging potential of carrot seed oil-based cosmetic emulsions. Briefly, cosmetic emulsions composed of carrot seed oil in varying proportions (2, 4, and 6% w/v) were prepared using the hydrophile-lipophile balance (HLB) technique. Coconut oil, nonionic surfactants (Tween 80 and Span 80), and xanthan gum were used as the oil phase, emulgent, and emulsion stabilizer, respectively.

<>The formed emulsions were evaluated for various physical, chemical, and biochemical parameters such as the zeta potential, globule size measurement, antioxidant activity, sun protection factor (SPF), skin irritation, and biochemical studies. The zeta potential values ranged from -43.2 to -48.3, indicating good stability.
<>The polydispersity index (PDI) of various emulsion formulations ranged from 0.353 to 0.816. 1,1-Diphenyl-2-picrylhydrazyl- (DPPH) and nitric oxide-free radical scavenging activity showed the antioxidant potential of the prepared carrot seed oil emulsions.
<>The highest SPF value (6.92) was shown by F3 having 6%w/v carrot seed oil. Histopathological data and biochemical analysis (ascorbic acid (ASC) and total protein content) suggest that these cosmetic emulsions have sufficient potential to be used as potential skin rejuvenating preparations."[471.0]

Eucalyptus Globulus oil (Cineole + other Chemical Constituents)

Eucalyptus Globulus oil (EO) in very low concentrations enhances Phagocytosis & Efferocytosis (the clearance of foreign cells or dead tissue), predominately due to the high concentration of Cineole.

[A] EO stimulates macrophage function in diverse ways, such as enhanced motility and enhanced phagocytosis / efferocytosis efficiency.

"<>We also obtained evidence indicating that EO might affect macrophage motility and chemotaxis by stimulating the assembly and disassembly of podosome structures. Indeed, EO stimulation significantly increases podosome density, as well as augmenting colocalization at the podosomes of the actin core with the ring component vinculin, which is known to function, together with talin and paxillin, as a linker between integrins and actin-associated proteins during podosome assembly. The augmented colocalization recorded suggests that EO could improve the actin-binding capacity of vinculin, but further study is required to deeply clarify this point. <>Furthermore, at early stages of treatment EO induces a moderate but significant increase in the expression levels of αM integrin (CD11b) and β2 (CD18) integrins. Since these integrins are not only two of the main structural components of the podosome ring that regulate the interaction between cell and extracellular matrix during cell movement but also form together the heterodimeric complex CD11b/CD18 (or CR3), this result provides further evidence that EO might stimulate podosome formation, macrophage motility, and the CR-mediated macrophagic functions. The Transwell migration assay confirmed that the essential oil can implement macrophage motility under a chemotactic stimulus.
<>These results are stimulating for future insights aimed to assess whether this essential oil could also be proposed as a possible adjuvant for those immunodeficiency disorders in which a reduced capacity or an inability to make podosomes severely prejudices the migration and chemotaxis of macrophages and monocytes"[471.1]

[A2] Macrophage activity decreases during aging, leading to increased risk of infection, dementia, and delayed wound regeneration.

“<>A growing body of evidence suggests that phagocyte dysfunction in aged tissues will lead to accumulation of unphagocytosed debris, deterioration of tissue homeostasis, imbalance of innate immune response, chronic sterile inflammation, and accelerated tissue damage and degeneration. Lack of knowledge on the molecular mechanisms of phagocyte aging has hindered our capability of developing anti-aging therapy by modulating phagocyte activity and preventing age-related tissue damage. New research tools developed in the past few years has enabled systematic identification of phagocytosis ligands in the absence of receptor information and reliable quantification of their functional activities. Quantitative comparison for young vs. aged phagocytes will identify age-dependent phagocytosis ligands and their signaling pathways. These will unravel the molecular mystery of phagocyte aging and dysfunction. Future therapies targeting age-dependent pathways can be developed to promote phagocyte function, restore tissue homeostasis and prevent or delay tissue degeneration.”[471.2]

Linalool (Lavender Angustifolia / Latifolia oil)

Linalool appears to prevent muscle atrophy with a slight risk of toxicity to muscle cells. Because of the very high estrogenic side effects, only females should apply it to their bodies, whereas infrequent inhalation in lean men will be likely okay. Interestingly, Spike Lavender AKA Lavender Latifolia has a high concentration of Linalool, Cineole, and Camphor, and may therefore be the best antiaging essential oil to apply to the skin.

“<>The results showed that LIN could prevent the myotube atrophy and poor differentiation induced by DDP, upregulate the expression of MyoG, MyoD and MyHC, and inhibit the expression of myostatin, Atrogin1, MuRF1 and ubiquitin." Importantly, when LIN activated the IGF-1/Akt/FoxO signaling pathway to inhiIn this study, the in vitro experimental doses of LIN used were mainly derived from the commonly used doses in other pharmacological studies of LIN, and the cytotoxic effect of various doses of LIN on C2C12 myoblasts and myotubes were verified through CCK8 assay. Ultimately, a dose that did not have serious effects on cell survival was selected for the experiments, that is, 25 μM.bit skeletal muscle degradation.”[472]

Eucalyptol (1,8-Cineole) / Camphor

[A] The study below describes how Eucalyptol and Camphor in low concentrations can promote DNA recombination (repair) in cells.

“<>The aim of this work was to examine the antigenotoxic potential of plant monoterpenes: camphor, eucalyptol and thujone in prokaryotic and eukaryotic cells and to elucidate their effect on DNA repair. We compared the effect of monoterpenes on spontaneous, UV- and 4NQO-induced mutagenesis in Escherichia coli K12 repair proficient, and MMR and NER deficient strains. Positive controls tannic acid and vanillin were included in bacterial tests. We also examined protective effect of monoterpenes

against 4NQO-induced genotoxicity in Vero cell line by alkaline comet assay. The results obtained in repair proficient strain indicated antimutagenic potential of monoterpenes against UV- and 4NQO-induced mutagenesis, which was diminished with NER deficiency.
<>Camphor and eucalyptol maintained UV-induced SOS response longer than in controls, while thujone decreased SOS response and reduced general protein synthesis and the growth rate. The three monoterpenes increased spontaneous and UV-induced recombination in recA730 and camphor additionally in recA(+) cells. Incubation of 4NQO-pretreated Vero cells with monoterpenes resulted in significant reduction of tail moment. However, higher concentrations of monoterpenes induced DNA strand breaks. Obtained results indicate that by making a small amount of DNA lesions camphor, eucalyptol and thujone can stimulate error-free DNA repair processes and act as bioantimutagens."[472.1]

[B] Camphor promotes collagen synthesis and may reduce or inhibit the growth of adipose tissue.

"<>Camphor ((1R)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-one), a bicyclic monoterpene, is one of the major constituents of essential oils from various herbs such as rosemary, lavender, and sage.
<>In this study, we investigated the beneficial effects of camphor as a botanical ingredient in cosmetics. Camphor induced the proliferation of human primary dermal fibroblasts in a dose-dependent manner via the PI3K/AKT and ERK signaling pathways. Camphor attenuated the elevation of senescence associated with β-galactosidase (SA-β-gal) activity. Elastase activity decreased, while the total amount of collagen increased, in a dose- and time-dependent manner in human primary dermal fibroblasts treated with camphor. Camphor induced the expression of collagen IA, collagen IIIA, collagen IVA, and elastin in human primary dermal fibroblasts.
<>In addition, posttreatment with 26 and 52 mM camphor for 2 weeks led to a significant reduction in the expression of MMP1 but increases in the expression of collagen IA, IIIA, and elastin in mouse skin exposed to UV for 4 weeks. These posttreatments also reduced the depths of the epidermis and subcutaneous fat layer in UV-exposed mouse skin. Taken together, these findings suggest camphor to be a potent wound healing and antiwrinkle agent with considerable potential for use in cosmeceuticals."[472.2]

!!CAUTION!! Topically-applied Capsaicin !!CAUTION!!

Capsaicin destroys different types of autonomic (sensory) nerves, which then regenerate to near-normal levels after a recovery period of several months.

"<>Objective: To determine the effects of topical application of capsaicin on cutaneous autonomic nerves. Methods: Thirty-two healthy subjects underwent occlusive application

of 0.1% capsaicin cream (or placebo) for 48 hours. Subjects were followed for 6 months with serial assessments of sudomotor, vasomotor, pilomotor, and sensory function with simultaneous assessment of innervation through skin biopsies.
<>Results: There were reductions in sudomotor, vasomotor, pilomotor, and sensory function in capsaicin-treated subjects ($p < 0.01$ vs. placebo). Sensory function declined more rapidly than autonomic function, reaching a nadir by Day 6, whereas autonomic function reached a nadir by Day 16. There were reductions in sudomotor, vasomotor, pilomotor, and sensory nerve fiber densities in capsaicin-treated subjects ($p < 0.01$ vs. placebo). Intraepidermal nerve fiber density declined maximally by 6 days, whereas autonomic nerve fiber densities reached maximal degeneration by Day 16. Conversely, autonomic nerves generally regenerated more rapidly than sensory nerves, requiring 40-50 days to return to baseline levels, whereas sensory fibers required 140-150 days to return to baseline.
<>Interpretation: Topical capsaicin leads to degeneration of sudomotor, vasomotor, and pilomotor nerves accompanied by impairment of sudomotor, vasomotor, and pilomotor function. These results suggest the susceptibility and/or pathophysiologic mechanisms of nerve damage may differ between autonomic and sensory nerve fibers treated with capsaicin and enhances the capsaicin model for the study of disease-modifying agents. The data suggest caution should be taken when topical capsaicin is applied to skin surfaces at risk for ulceration, particularly in neuropathic conditions characterized by sensory and autonomic impairment."[473]

Myostatin

Myostatin is a member of TGF-b superfamily, it is a genetic suppressor of myogenesis, but positively associates with tendon health & muscle force production.
IGF-1 associates with fast twitch fibers in the absence of Myostatin, leading to the view that Myostatin plays a large role in slow twitch fiber formation.
Growing up, being a subscriber of the biggest bodybuilding magazines, I was fooled into thinking that Myostatin inhibition was the future and endpoint of myogenic facilitation, but the truth is far more complex than was advertised.
[Note: Mechano Growth Factor (MGF) is a splice variant of IGF-1]

[A] Myostatin knockout mice have brittle tendons. Therefore, Myostatin inhibition comes with dire consequences.

"<>Tendons play a significant role in the modulation of forces transmitted between bones and skeletal muscles and consequently protect muscle fibers from contraction-induced, or high-strain, injuries. Myostatin (GDF-8) is a negative regulator of muscle mass. Inhibition of myostatin not only increases the mass and maximum isometric force of muscles, but also increases the susceptibility of muscle fibers to contraction-induced injury. We hypothesized that myostatin would regulate the morphology and mechanical properties of tendons.

<>The expression of myostatin and the myostatin receptors ACVR2B and ACVRB was detectable in tendons. Surprisingly, compared with wild type (MSTN(+/+)) mice, the tendons of myostatin-null mice (MSTN(-/-)) were smaller and had a decrease in fibroblast density and a decrease in the expression of type I collagen. Tendons of MSTN(-/-) mice also had a decrease in the expression of two genes that promote tendon fibroblast proliferation: scleraxis and tenomodulin. Treatment of tendon fibroblasts with myostatin activated the p38 MAPK and Smad2/3 signaling cascades, increased cell proliferation, and increased the expression of type I collagen, scleraxis, and tenomodulin. Compared with the tendons of MSTN(+/+) mice, the mechanical properties of tibialis anterior tendons from MSTN(-/-) mice had a greater peak stress, a lower peak strain, and increased stiffness.
<>We conclude that, in addition to the regulation of muscle mass and force, myostatin regulates the structure and function of tendon tissues."[474.0]

[B] Myostatin is associated with suppressed fast twitch fiber growth, and therefore it could be said that Myostatin promotes the slow twitch phenotype indirectly.

"<>Insulin-like growth factors (IGFs) and myostatin have opposing roles in regulating the growth and size of skeletal muscle, with IGF1 stimulating, and myostatin inhibiting, growth. However, it remains unclear whether these proteins have mutually dependent, or independent, roles. To clarify this issue, we crossed myostatin null (Mstn-/-) mice with mice overexpressing Igf1 in skeletal muscle (Igf1+) to generate six genotypes of male mice; wild type (Mstn+/+), Mstn+/-, Mstn-/-, Mstn+/+:Igf1+, Mstn+/-:Igf1+ and Mstn-/-:Igf1+ Overexpression of Igf1 increased the mass of mixed fibre type muscles (e.g. Quadriceps femoris) by 19% over Mstn+/+ , 33% over Mstn+/- and 49% over Mstn-/- ($P < 0.001$).
<>By contrast, the mass of the gonadal fat pad was correspondingly reduced with the removal of Mstn and addition of Igf1 Myostatin regulated the number, while IGF1 regulated the size of myofibres, and the deletion of Mstn and Igf1+ independently increased the proportion of fast type IIB myosin heavy chain isoforms in T. anterior (up to 10% each, $P < 0.001$). The abundance of AKT and rpS6 was increased in muscles of Mstn-/-mice, while phosphorylation of AKTS473 was increased in Igf1+mice (Mstn+/+:Igf1+, Mstn+/-:Igf1+ and Mstn-/-:Igf1+).
<>Our results demonstrate that a greater than additive effect is observed on the growth of skeletal muscle and in the reduction of body fat when myostatin is absent and IGF1 is in excess. Finally, we show that myostatin and IGF1 regulate skeletal muscle size, myofibre type and gonadal fat through distinct mechanisms that involve increasing the total abundance and phosphorylation status of AKT and rpS6."[474]

[C] Myostatin is required for muscle force production, and its ablation promotes fast twitch fiber growth. It is quite strange that Myostatin reduces fast twitch fiber growth, but

is necessary for muscle force output, although this is possibly because it interacts with the ECM, as it has been shown to promote muscle fibrosis.

"<>The lack of myostatin promotes growth of skeletal muscle, and blockade of its activity has been proposed as a treatment for various muscle-wasting disorders. Here, we have examined two independent mouse lines that harbor mutations in the myostatin gene, constitutive null (Mstn(-/-)) and compact (Berlin High Line, BEH(c/c)). We report that, despite a larger muscle mass relative to age-matched wild types, there was no increase in maximum tetanic force generation, but that when expressed as a function of muscle size (specific force), muscles of myostatin-deficient mice were weaker than wild-type muscles.
<>In addition, Mstn(-/-) muscle contracted and relaxed faster during a single twitch and had a marked increase in the number of type IIb fibers relative to wild-type controls. This change was also accompanied by a significant increase in type IIB fibers containing tubular aggregates. Moreover, the ratio of mitochondrial DNA to nuclear DNA and mitochondria number were decreased in myostatin-deficient muscle, suggesting a mitochondrial depletion. Overall, our results suggest that lack of myostatin compromises force production in association with loss of oxidative characteristics of skeletal muscle."[475]

[D] Myostatin reduces hypertrophy but is not toxic to muscle cells, an interesting piece of information.

"<>During myogenesis, myoblasts proliferate and withdraw from the cell cycle and commit to a differentiation pathway to form myotubes. The size of muscle, therefore, is in part dependent on the extent of myoblast proliferation that occurs prior to differentiation. Recent studies show that myostatin inhibits the proliferation of exponentially growing myoblasts in culture without causing overt differentiation or increasing apoptotic cell death."[476]

Microcurrent Electrotherapy

This novel myogenic therapy is intriguing, and may well be pseudoscience at best, which is why I have included it at near-to-the-end of my book. Research or utilize this science at your own risk, albeit I can inform you that higher current electrotherapy such as TENS unit therapy has deleterious effects on post-therapy muscle force generation, the difference is substantial as MENS is microamperes, and TENS is milliamperes, for comparison: 1 Milliampere (mA) = 1000 Microampere (µA). The research suggests using between 5-50 µA to achieve an effect.

[A] Microcurrent Therapy promotes muscle regeneration.

"<>In a previous study, when electric currents with 10–50 μA amplitude were used to treat muscle-related problems, different microcurrent machines were used. Previous studies demonstrated that MT with low amperage electric current of < 500 mA could reduce the severity of muscle symptoms. These electric current intensities are within the therapeutic range, which is optimum for ATP generation. These results are consistent with the findings of the current study and suggest that low-amperage electric currents can more effectively improve skeletal muscle regeneration than high-amperage electric currents.
<>Notably, the results of the present study showed that, compared with the effect of high-intensity MT, lowintensity MT can remarkably facilitate the regeneration of immobilised skeletal muscles through stimulating the proliferative potential of muscle satellite cells, instead of simply influencing the remobilisation of skeletal muscles. In addition, no adverse effects or untoward events were observed during the study, because MT worked at the microampere level and mimicked the electrical intensity found in the living tissue."[476.1]

[B] TENS unit therapy (mA), reduces muscle force output. This may be due to temporary or long lasting, but surely not permanent intra-muscular synaptic changes. This study means that TENS unit therapy, as popularized by the fitness community currently, is useless for the promotion of muscle performance.

"<>Methods: Thirty-six participants were randomized to a TENS treatment, TENS placebo, or control group after completing a standardized DOMS protocol. Measures included shoulder strength, pain, mechanical pain sensitivity, and disability. TENS treatment and TENS placebo groups received 90 minutes of active or sham treatment 24, 48, and 72 hours post-DOMS. All participants were assessed daily.
<>Results: A repeated measures analysis of variance and post-hoc analysis indicated that, compared to the control group, strength remained reduced in the TENS treatment group (48 hours post-DOMS, $P < 0.05$) and TENS placebo group (48 hours post-DOMS, $P < 0.05$; 72 hours post-DOMS, $P < 0.05$). A mixed-linear modeling analysis was conducted to examine the strength (motor) change. Randomization group explained 5.6% of between-subject strength variance ($P < 0.05$). Independent of randomization group, pain explained 8.9% of within-subject strength variance and disability explained 3.3% of between-subject strength variance (both $P < 0.05$).
<>Discussion: While active and placebo TENS resulted in prolonged strength inhibition, the results were nonsignificant for pain. Results indicated that higher pain and higher disability were independently related to decreased strength. Regardless of the impact on pain, TENS, or even the perception of TENS, may act as a nocebo for motor output."[476.2]

Unmentioned Amino Acids, Protein, & Ammonia

In terms of each individual amino acid, they are all important for myogenesis, neurogenesis, & lipolysis, especially non-proteinogenic ones, such as Ornithine, & Citrulline, which are often neglected in the fitness community. I suggest you follow the common edict of consuming 2-4g of Lean Meat Protein per kilogram of bodyweight per day, but for the elderly, sickly, terminally busy, or lazy, setting aside twenty or thirty minutes every three hours to eat is a ridiculous proposition, I would thus suggest consuming a 25g protein shake as a meal replacement every three hours, even with a meal, to ensure protein synthesis remains high.

Speaking of protein shakes, consuming faster digesting protein, such as in a shake containing Whey Isolate with each meal is one tactic to enhance the anabolism of a meal through Hyperaminoacidemia.

Comparing commonly sold protein powders, Whey Isolate has the most balanced and potent amino acid profile, therefore I will suggest its use over other protein powders, excluding casein, which owing to slower digestion is in a different category.

Looking at the variable but predictable amino acid profile of Whey Isolate we see that Methionine, Tryptophan, Tyrosine, Glycine, Cysteine, and Histidine are found in low concentrations (not including Arginine which will irritate the gastrointestinal tract in large concentrations). To therefore make a perfect protein powder, we should seek to balance the amino acid profile of our chosen protein powder by adding raw aminos to it. The only issue that presents itself with adding raw aminos to protein powder is the difference in pharmacokinetics, in that the amino acids in protein powder will clearly reach systemic circulation slower than any raw amino acids that are added to it. This leads me to the conclusion that certain raw aminos (see previous list) should be sipped intra-workout, excluding glycine which should already be present in the blood in adequate concentrations [See: GlySer], after consuming a large amount of protein powder pre-workout. Therefore, you will have your Pre / Post-workout protein shake, and your intra-workout aminos.

Here are some studies you might be unaware of:

[A] Pre-Workout Protein (because it digests slowly) boosts anabolism much more than post. Raw Aminos or Hydrolyzed Protein powders will work more effectively than Whey Isolate if consumed Intra-Workout but timing your Whey Isolate shakes to one hour Pre-Workout (Shake #1), Immediately Pre-Workout (Shake #2), and Post-Workout (Shake #3) will work similarly.

"<>The present study was designed to determine whether consumption of an oral essential amino acid-carbohydrate supplement (EAC) before exercise results in a greater anabolic response than supplementation after resistance exercise. Six healthy human subjects participated in two trials in random order, PRE (EAC consumed immediately before exercise), and POST (EAC consumed immediately after exercise). A primed,

continuous infusion of L-phenylalanine, femoral arteriovenous catheterization, and muscle biopsies from the vastus lateralis were used to determine phenylalanine concentrations, enrichments, and net uptake across the leg.
<>Blood and muscle phenylalanine concentrations were increased by approximately 130% after drink consumption in both trials. Amino acid delivery to the leg was increased during exercise and remained elevated for the 2 h after exercise in both trials. Delivery of amino acids (amino acid concentration times blood flow) was significantly greater in PRE than in POST during the exercise bout and in the 1st h after exercise ($P < 0.05$). Total net phenylalanine uptake across the leg was greater ($P = 0.0002$) during PRE (209 +/- 42 mg) than during POST (81 +/- 19).
<>Phenylalanine disappearance rate, an indicator of muscle protein synthesis from blood amino acids, increased after EAC consumption in both trials. These results indicate that the response of net muscle protein synthesis to consumption of an EAC solution immediately before resistance exercise is greater than that when the solution is consumed after exercise, primarily because of an increase in muscle protein synthesis as a result of increased delivery of amino acids to the leg."[477]

[B] Amino acids stimulate insulin release; this is especially relevant to those who wish to facilitate lipolysis maximally.

"<>The importance of amino acid-stimulated insulin secretion (AASIS) by pancreatic islets has long been recognized, but its mechanisms of action remain poorly understood. Studies on perfused rat islets in the 1970s found that many amino acids can only stimulate insulin secretion in the presence of glucose. These glucose-dependent amino acids include complete mixtures of all 20 amino acids as well as certain individual amino acids including alanine, asparagine, glycine, glutamate, phenylalanine, and tryptophan. Leucine is a notable exception to the rule that glucose is required for AASIS, since the insulin-stimulatory effect of leucine in perfused rat pancreas is abolished in the presence of glucose. In the 1980s, Sener and Malaisse showed that leucine stimulates insulin secretion by allosterically stimulating glutamate dehydrogenase (GDH) activity."[478]

[C] BCAA's alone are not enough to stimulate protein synthesis, and in fact reduce it by limiting EAA recycling (protein synthesis). All Essential Amino Acids must be consumed to maintain a higher rate of protein synthesis. Furthermore, because amino acids compete with each other for entry into cells, consuming large dosages of Leucine alone (fasted) will most likely exert a more pronounced anabolic effect on slow twitch fiber growth.

"<>Louard et al. used the forearm balance method to quantify the response to the intravenous infusion of a mixture of BCAAs for 3 h in 10 post-absorptive subjects. The forearm balance method involves the measurement of the uptake and release of individual EAAs (leucine and phenylalanine in this case) and their isotopically-labelled counterparts. Rates of disappearance (Rd) and appearance (Ra) of phenylalanine and

leucine are calculated. With the assumption that the balance across the muscle of leucine and phenylalanine is representative of all EAAs, Rd. of phenylalanine is taken to be a reflection of muscle protein synthesis, since protein synthesis is the only fate of phenylalanine taken up by muscle from plasma.
<>The Rd. of leucine cannot be interpreted with regard to protein synthesis, as leucine taken up by muscle can be oxidized as well as incorporated into protein. The 3 h infusion of BCAAs increased plasma concentrations of all 3 BCAAs four-fold, while the concentrations of other EAAs decreased. Rather than being stimulated by the BCAA infusion, muscle protein synthesis decreased from 37+/− 3 to 21 +/− 2 nmol/min/100 ml leg (statistically significant, $p < 0.05$).
<>There was no significant change in net phenylalanine balance, indicating that muscle protein breakdown was also reduced an amount similar to the reduction in muscle protein synthesis. The balance between muscle protein synthesis and breakdown remained negative, meaning that the catabolic state persisted, and an anabolic state was not produced. The simultaneous decreases in muscle protein synthesis and breakdown during BCAA infusion can be described as decreased muscle protein turnover.
<>When all evidence and theory is considered together, it is reasonable to conclude that there is no credible evidence that ingestion of a dietary supplement of BCAAs alone results in a physiologically-significant stimulation of muscle protein. In fact, available evidence indicates that BCAAs actually decrease muscle protein synthesis. All EAAs must be available in abundance for increased anabolic signaling to translate to accelerated muscle protein synthesis.
<>While a dietary supplement with all of the BCAAs will overcome the decreases in concentration resulting from consumption of leucine alone, the addition of valine and isoleucine may nonetheless limit the effectiveness of leucine alone due to competition for transport into muscle cells. The BCAAs are all actively transported into cells, including muscle cells, by the same transport system. Therefore, when provided together the BCAAs compete with each other for transport into the cells. If one of the BCAAs (e.g., leucine) is rate limiting for protein synthesis, addition of the other two BCAAs might limit the stimulation of protein synthesis because of reduced entry of leucine into the cell. The BCAAs also compete with other amino acids for transport, including phenylalanine, and this competition could affect the intramuscular availability of other EAAs. As a result of competition for transporters, it is possible that leucine alone, for example, could have a transitory stimulatory effect on muscle protein synthesis (where the BCAAs fail to elicit such response).”[479]

[C2] Chronic Leucine supplementation post-slow twitch muscle injury reduces muscle fibroses (TGF / Smad), and more interestingly it appears that Leucine is a slow twitch amino acid, meaning consuming massive amounts of Leucine each day may increase Strength-Endurance, but it will not influence muscular Power-Explosivity, this therefore dispels the old bodybuilding belief that Leucine is the “Anabolic Trigger of mTOR” and

essential for muscle growth. Considering β-Hydroxy β-Methylbutyrate (HMB) is a metabolic breakdown product of Leucine, it would make sense to combine Leucine and HMB on slow twitch focused protocols, while restricting all other essential and non-essential amino acids (for short periods of time, such as six hours, or twelve hours per day).

"<>This study investigated the effect of leucine supplementation on the skeletal muscle regenerative process, focusing on the remodeling of connective tissue of the fast twitch muscle tibialis anterior (TA). Young male Wistar rats were supplemented with leucine (1.35 g/kg per day); then, TA muscles from the left hind limb were cryolesioned and examined after 10 days.
<>Although leucine supplementation induced increased protein synthesis, it was not sufficient to promote an increase in the cross-sectional area (CSA) of regenerating myofibers ($p > 0.05$) from TA muscles. However, leucine supplementation reduced the amount of collagen and the activation of phosphorylated transforming growth factor-β receptor type I (TβR-I) and Smad2/3 in regenerating muscles ($p < 0.05$). Leucine also reduced neonatal myosin heavy chain (MyHC-n) ($p < 0.05$), increased adult MyHC-II expression ($p < 0.05$) and prevented the decrease in maximum tetanic strength in regenerating TA muscles ($p < 0.05$).
<>Our results suggest that leucine supplementation accelerates connective tissue repair and consequent function of regenerating TA through the attenuation of TβR-I and Smad2/3 activation. Therefore, future studies are warranted to investigate leucine supplementation as a nutritional strategy to prevent or attenuate muscle fibrosis in patients with several muscle diseases."
↓ continued
"<>Leucine supplementation alone did not cause a significant increase in the size of myofibers from uninjured TA, which may result from an unaltered rate of protein synthesis and the consequent unchanged expression of MyHC-II observed in our study. These results are in line with the finding that the combination of leucine and glucose supplementation significantly increases tyrosine incorporation into proteins in vitro preferentially in fasted slow twitch muscles, such as the diaphragm and soleus, and no effect is detectable in the fasted fast twitch muscle, gastrocnemius. The greater effect of leucine on slow twitch muscle may be related to its more efficient metabolization than in fast twitch muscles."[479.0]
[D] Leucine starvation reduces MyoD activity while increasing Myf5, with MyoD being more vital to the process of Myogenesis than Myf5.

"<>Satellite cells are the major pool of muscle stem cells after birth; they represent an important component required to maintain muscle mass and functionality during life. The molecular mechanisms involved in myogenic differentiation are relatively well-known.

However, the role of extracellular stimulus in the control of differentiation remains largely unresolved. Notably little is known about the impact of nutrients on this process. <>Here we have studied the role of leucine, an essential amino acid, in the control of myogenic differentiation. Leucine is a well-known regulator of muscle protein synthesis. It acts not only as a substrate for translation but also as a regulator of gene expression and signaling pathways such as those involving mTOR and GCN2. In this study we demonstrated that the lack of leucine abolishes the differentiation of both C2C12 myoblasts and primary satellite cells.
<>This effect is associated with a modification of the pattern of expression of the myogenic regulatory factors (MRF) myf5 and myoD. We report an up-regulation of myf5 mRNA and a decrease of myoD protein level during leucine starvation. This study demonstrates the importance of a nutrient, leucine, in the control of the myogenic differentiation program."[479.1]

[E] Isoleucine may be anabolic, but it is also adipogenic.

"<>Isoleucine (Ile), as a branched-chain amino acid (BCAA), has a vital role in regulating body weight and muscle protein synthesis. However, the regulatory effect of Ile on muscle mass under high-fat diet (HFD) conditions and intramyocellular lipid deposition remains largely unclear. In this study, a feeding experiment with HFD with or without 25 g L-1 Ile was performed using 32 wild male C57BL/6J mice randomly divided into two groups.
<>The results showed that Ile significantly increased both muscle and fat mass, as well as causing insulin resistance and meanwhile upregulating the levels of key adipogenic and myogenic proteins. More importantly, Ile damaged the mitochondrial function by vacuolation, swelling and cristae fracture in the gastrocnemius (GAS) and tibialis anterior (TA) with downregulation of mitochondrial function-related genes. Furthermore, Ile promoted myogenesis and more lipid droplet accumulation in myotubes.
<>Compared with the control, the protein levels of myosin heavy chain (MyHC), myoblast determination protein 1 (MyoD), myogenin (MyoG), peroxisome proliferator-activated receptor gamma (PPARg) and fatty acid synthase (FAS) were upregulated in the Ile group, whereas the protein levels of adipose triglyceride lipase (ATGL) and lipoprotein lipase (LPL) were downregulated. Collectively, Ile increased muscle mass through myogenesis and intramyocellular lipid deposition. Our findings provide a new perspective for not only improving the lean juiciness of farm animals by increasing intramyocellular lipid accumulation, but also modulating myopathies under obesity."[479.2]

[F] The Valine breakdown product 3HIB reduces insulin sensitivity.

"<>Branched-chain amino acids (BCAAs) are essential in the diet and may provide benefit for those who partake in regular physical activity and resistance training, yet

circulating BCAAs have been repeatedly shown to correlate with severity of insulin resistance in obese/diseased populations. Recently, the valine catabolite 3-hydroxyisobuterate (3HIB) was shown to promote insulin resistance in skeletal muscle by increasing lipid content in vivo.
<>The purpose of this study was to investigate the mechanistic effects of 3HIB on skeletal muscle insulin signaling, metabolism, and related gene expression in vitro. Given these previous observations, we hypothesized that 3HIB would depress skeletal muscle metabolism and insulin sensitivity. C2C12 myotubes were treated with 3HIB for up to 48 hours using both physiological (25-100 μmol/L) and supraphysiological (5 mmol/L) concentrations. Metabolic gene expression was measured via quantitative real-time polymerase chain reaction, mitochondrial metabolism was measured via O2 consumption, and glycolytic metabolism was quantified using extracellular acidification rate. Western blot was used to assess insulin sensitivity following insulin stimulation (indicated by phospho-AKT expression).
<>3HIB did not alter expressional indicators of mitochondrial biogenesis, glycolysis, BCAA catabolism, or lipogenesis. Chronic physiological 3HIB treatment significantly increased peak oxygen consumption, whereas supraphysiological 3HIB treatment suppressed basal and peak mitochondrial and glycolytic metabolism. Both physiological and supraphysiological 3HIB reduced pAkt expression during insulin stimulation. These findings suggest that 3HIB may reduce muscle insulin sensitivity in cultured myotubes, supporting a potentially causal role of 3HIB in the development of insulin resistance in highly metabolic cell types."[479.3]

[G] Leucine reduces AMPK thereby promoting mTOR expression. Taking this information into account with the previously mentioned & following research, adding extra Leucine to a post-workout protein shake may exert a potent anabolic effect on myogenesis due to enhancing the association between Rheb-mTORC1.

[G2] "<>Mammalian target of rapamycin (mTOR) signaling is one of the main signaling pathways controlling protein synthesis. Leucine treatment upregulates mTOR signaling, which enhances protein synthesis; however, the mechanisms are not well understood. Herein, treatment of C2C12 myoblast cells with leucine enhanced the phosphorylation of mTOR and ribosomal protein S6 kinase. Leucine treatment also decreased the adenosine monophosphate/ATP ratio in myoblasts by 36.4 +/- 9.1% ($P < 0.05$) and reduced the phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) alpha subunit at Thr172 (28.6 +/- 4.9% reduction, $P < 0.05$) and inhibited AMPK activity (43.6 +/- 3.5% reduction, $P < 0.05$).
<>In addition, leucine increased the phosphorylation of mTOR at Ser2448 by 63.5 +/- 10.0% ($P < 0.05$) and protein synthesis by 30.6 +/- 6.1% ($P < 0.05$). Applying 5-aminoimidazole-4-carbox-amide 1-beta-d-ribonucleoside, an activator of AMPK,

abolished the stimulation of mTOR signaling by leucine, showing that AMPK negatively controls mTOR signaling.
<>To further show the role of AMPK in mTOR signaling, myoblasts expressing a dominant negative AMPKalpha subunit were employed. Negative myoblasts had very low AMPK activity. The activation of mTOR induced by leucine in these cells was abated, showing that AMPK contributed to mTOR activation. In conclusion, leucine stimulates mTOR signaling in part through AMPK inhibition. This study implicates AMPK as an important target for nutritional management to enhance mTOR signaling and protein synthesis in muscle cells, thereby increasing muscle growth."[479.4]

[G3] "<>Postexercise protein ingestion can elevate rates of myofibrillar protein synthesis (MyoPS), mTORC1 activity, and mTOR translocation/protein-protein interactions. However, it is unclear if leucine-enriched essential amino acids (LEAA) can similarly facilitate intracellular mTOR trafficking in humans after exercise. The purpose of this study was to determine the effect of postexercise LEAA (4 g total EAAs, 1.6 g leucine) on acute MyoPS and mTORC1 translocation and signaling. Recreationally active men performed lower-body resistance exercise (5 × 8-10 leg press and leg extension) to volitional failure.
<>Following exercise participants consumed LEAA (n = 8) or an isocaloric carbohydrate drink (PLA; n = 10). MyoPS was measured over 1.5-4 h of recovery by oral pulse of l-[*ring*-$^{2}H_5$]-phenylalanine. Phosphorylation of proteins in the mTORC1 pathway were analyzed via immunoblotting and mTORC1-LAMP2/WGA/Rheb colocalization via immunofluorescence microscopy. There was no difference in MyoPS between groups (LEAA = 0.098 ± 0.01%/h; PL = 0.090 ± 0.01%/h; $P > 0.05$). Exercise increased ($P < 0.05$) rpS6$^{Ser240/244}$(LEAA = 35.3-fold; PLA = 20.6-fold), mTOR^{Ser2448}(LEAA = 1.8-fold; PLA = 1.2-fold) and 4EBP1$^{Thr37/46}$(LEAA = 1.5-fold; PLA = 1.4-fold) phosphorylation irrespective of nutrition ($P > 0.05$). LAT1 and SNAT2 protein expression were not affected by exercise or nutrient ingestion. <>mTOR-LAMP2 colocalization was greater in LEAA preexercise and decreased following exercise and supplement ingestion ($P < 0.05$), yet was unchanged in PLA. mTOR-WGA (cell periphery marker) and mTOR-Rheb colocalization was greater in LEAA compared with PLA irrespective of time-point ($P < 0.05$).
<>In conclusion, the postexercise consumption of 4 g of LEAA maintains mTOR in peripheral regions of muscle fibers, in closer proximity to its direct activator Rheb, during prolonged recovery independent of differences in MyoPS or mTORC1 signaling compared with PLA ingestion. This intracellular localization of mTOR may serve to "prime" the kinase for future anabolic stimuli.
<>NEW & NOTEWORTHY This is the first study to investigate whether postexercise leucine-enriched amino acid (LEAA) ingestion elevates mTORC1 translocation and protein-protein interactions in human skeletal muscle. Here, we observed that although LEAA ingestion did not further elevate postexercise MyoPS or mTORC1 signaling

compared with placebo, mTORC1 peripheral location and interaction with Rheb were maintained. This may serve to "prime" mTORC1 for subsequent anabolic stimuli."[479.5]

[H] Dietary protein intake beyond the recommended suggestions does enhance muscle growth. To me the explanation of this is simple; Although there may be a hypothetical dosage limit to an amino acids' anabolic effect on muscle tissue, food "protein" is not a uniform spread of amino acids, it is a mixture of varying concentrations of different amino acids. Therefore, the Proteins found in foods and drinks are not to be thought of as structured and static, they are composed of many concentrations of many different interlinked amino acids.

Finding out what amino acids are found in low concentrations in your daily meat or protein powders, and supplementing them, is a good tactic to promote protein synthesis. Furthermore, changing or mixing together different meats or other protein sources in each meal is another good tactic to promote protein synthesis, for the obvious reason that the amino acid profiles of different foods will always differ. Although most protein powders tend to be low in Cysteine, Methionine, and Tryptophan, making it a better idea to buy these chemicals in bulk powders and add them to an intra-workout drink, or Pre/Post-Workout Protein Drink.

"<>We have determined whole body protein kinetics, i.e., protein synthesis (PS), breakdown (PB), and net balance (NB) in human subjects in the fasted state and following ingestion of ~40 g [moderate protein (MP)], which has been reported to maximize the protein synthetic response or ~70 g [higher protein (HP)] protein, more representative of the amount of protein in the dinner of an average American diet. <>Twenty-three healthy young adults who had performed prior resistance exercise (X-MP or X-HP) or time-matched resting (R-MP or R-HP) were studied during a primed continuous infusion of l-[2H5]phenylalanine and l-[2H2]tyrosine. Subjects were randomly assigned into an exercise (X, n = 12) or resting (R, n = 11) group, and each group was studied at the two levels of dietary protein intake in random order. PS, PB, and NB were expressed as increases above the basal, fasting values (mg·kg lean body mass−1·min−1). Exercise did not significantly affect protein kinetics and blood chemistry.
<>Feeding resulted in positive NB at both levels of protein intake: NB was greater in response to the meal containing HP vs. MP ($P < 0.00001$). The greater NB with HP was achieved primarily through a greater reduction in PB and to a lesser extent stimulation of protein synthesis (for all, $P < 0.0001$). HP resulted in greater plasma essential amino acid responses ($P < 0.01$) vs. MP, with no differences in insulin and glucose responses. In conclusion, whole body net protein balance improves with greater protein intake above that previously suggested to maximally stimulating muscle protein synthesis because of a simultaneous reduction in protein breakdown."[479.6]

Hyperaminoacidemia

We are taught both consciously and unconsciously that to build muscles, massive amounts of slower digesting proteins must be consumed, to ensure that muscle protein synthesis increases and never wanes, but we are misled by a partial truth. While it is true that eating chronic amounts of slow digesting (meat) protein meals on a high frequency timed meal protocol will result in noticeable increases in protein synthesis, this is not because the protein is *slow* digesting, it is because it is *simply protein*, and the greater amount of slow digesting protein one consumes at one time, the greater the rise in blood amino acids will occur over the course of the next few hours. Contrary to popular belief, what builds muscle is not slow digesting protein meals, it is *meal protein potency x meal protein frequency*, with the former being of the utmost anabolic importance, for it is the condition of Hyperaminoacidemia (and Leucinaemia) that builds muscle[1], even if it is a temporal condition experienced in average individuals. The latter, meal frequency, is of necessity to maximize the benefits of Hyperaminoacidemia over time, and because most, if not all bodybuilders eat every three hours, this explains why many believe food is more anabolic than protein powders.

In the end it is more logical to suggest that regarding dietary protein, a protein source coming from protein powder, which is faster digesting, if consumed every two-three hours, especially alongside slow digestion protein (meat / cheese) will increase protein synthesis to a greater extent than consuming an equal or doubled amount of protein found in meat, especially if two or more exercise sessions are performed in a day, wherein the metabolism desperately seeks Hyperaminoacidemia to magnify the earliest myogenic signaling, and thus in the case of pre/post-workout protein choice, a giant chicken breast just doesn't cut it.

Consuming a Whey Isolate (or any other fast digesting protein powder) shake of 10-25g every three hours with a slow protein meal will likely give you the anabolic boost you so seek, at the cost of increased insulin release (Akt pathway activity)[2].

[1] "<>We aimed to determine the effect of consuming pure isolated micellar casein or pure whey protein isolate on rates of myofibrillar protein synthesis (MPS) at rest and after resistance exercise in elderly men.
<>Healthy elderly men (72 (sem 1) years; BMI 26·4 (sem 0·7) kg/m²) were divided into two groups (n 7 each) who received a primed, constant infusion of l-[ring-$^{13}C_6$]phenylalanine to measure MPS at rest and during 4 h of exercise recovery. Participants performed unilateral leg resistance exercise followed by the consumption of isonitrogenous quantities (20 g) of casein or whey.
<>Blood essential amino acids and leucine concentration peaked 60 min post-drink and were greater in amplitude after whey protein ingestion (both, $P < 0·05$). MPS in the rested leg was 65 % higher ($P = 0·002$) after ingestion of whey (0·040 (sem 0·003) %/h) when compared with micellar casein (0·024 (sem 0·002) %/h). Similarly, resistance

exercise-stimulated rates of MPS were greater ($P < 0{\cdot}001$) after whey ingestion (0·059 (sem 0·005) %/h) v. micellar casein (0·035 (sem 0·002) %/h). We conclude that ingestion of isolated whey protein supports greater rates of MPS than micellar casein both at rest and after resistance exercise in healthy elderly men. This result is probably related to a greater hyperaminoacidaemia or leucinaemia with whey ingestion."[479.6.1]

[2] "<>Protein ingestion concurrently stimulates euglycemic glucagon and insulin secretion, a response that is particularly robust with rapidly absorbing proteins. Previously, we have shown that ingestion of repeated doses of rapidly absorbing whey protein equally stimulated endogenous glucose production (EGP) and glucose disposal (Rd), thus explaining the preservation of euglycemia.
<>Here, we aimed to determine if a smaller single dose of whey could elicit a large enough glucagon and insulin response to stimulate glucose flux. Therefore, in normoglycemic young adult males (n = 10; age ∼26; BMI ∼25), using [6,6-$^2H_2$] glucose tracing and quantitative targeted metabolite profiling, we determined the metabolic response to a single 25 g "standard" dose of whey protein. Whey protein ingestion did not alter glycemia, but increased circulating glucagon (peak 4-fold basal), insulin (peak 6-fold basal), amino acids, and urea while also reducing free fatty acid (FFA) and glycerol concentrations.
<>Interestingly, the postprandial insulin response was driven by both a stimulation of insulin secretion and marked reduction in hepatic insulin clearance. Whey protein ingestion resulted in a modest stimulation of EGP and Rd, both peaking at ∼20% above baseline 1 h after protein ingestion. These findings demonstrate that the ingestion of a single standard serving of whey protein can induce a euglycemic glucagon and insulin response that stimulates glucose flux. We speculate on a theory that could potentially explain how glucagon and insulin synergistically provide hardwired control of nitrogen and glucose homeostasis.
<>NEW & NOTEWORTHY: Protein ingestion concurrently stimulates glucagon and insulin secretion. Here we show that in normoglycemic males, ingestion of a single "standard" 25 g serving of rapidly absorbing whey protein drives a sufficiently large glucagon and insulin response, such that it simultaneously increases endogenous glucose production and glucose disposal. We speculate on a novel theory that could potentially explain how the antagonistic/synergistic actions of glucagon and insulin simultaneously provide tight control of glucose and nitrogen homeostasis."[479.6.2]

Ammonia

Ammonia is a toxic chemical produced in our liver through amino acid metabolism, called deamination. During detoxification in the liver, Ammonia is converted into urea, a less toxic byproduct, which in then excreted through the urine.

A diet of excess protein increases blood ammonia[A], and strenuous endurance training increases muscle ammonia levels[B]. Caffeine appears to be the safest ammonia detoxifier[C]. And Carbohydrate Restriction may decrease ammonia production through interacting with an important liver enzyme[D].

[A] "<>Our model predicts that blood ammonia levels will rise slightly by consumption of a high protein diet. Surprisingly, we could not find many studies in the literature examining dietary-induced changes in blood ammonia levels in healthy humans. One study found increased blood ammonia levels in women following consumption of a test drink containing whey protein. The ammonia level peaked at a value 20% higher than the initial level at 90 min after consumption. Another study found increasing breath ammonia levels after a high protein challenge; ammonia levels plateaued roughly 5 h after the dietary challenge. However, breath ammonia levels do not always correlate well with blood ammonia levels. A further study using Huntington's disease patients who were put on a high (26.3%) protein diet did not find any association between the high protein diet and blood ammonia levels.
<>In studies with mice placed on a high protein diet, ammonia levels increased from 210 μM to 245 μM at night when the mice were active and feeding. Likewise, a high fat/low protein diet decreased ammonia levels from 170 μM to 130 μM when measured at night. When rats were switched from a 20% protein diet to a 58% protein diet, colonic venous ammonia maximally increased from 100 μM to 340 μM 2 days after the switch in diet, which dropped to 170 μM after a week on the diet. Another study using rats trained on a 6% protein diet showed that blood ammonia levels increased from 60 μM to 120 μM when they were given a 44% protein meal, and ammonia levels were maintained at that elevated level for at least 24 h. There is also evidence of increases in blood ammonia levels in pigs after a protein meal.
<>The limited data above suggest that systemic ammonia levels likely increase slightly following a meal, especially if the meal is high in protein, but more experiments should be performed to verify these initial findings and to determine the extent of brain ammonia level changes under the same conditions. In addition, more detailed studies using human subjects would help to better characterize the time dependency of elevated ammonia levels as well as to discern differential effects in patients with liver disease."[479.7]
[B] "<>In a number of individual cycling tests lasting 2.5-5 h with alternating exercise intensities of 50%-85% of maximal working capacity, it was observed that plasma ammonia levels may rise above 250 mumol/l when reaching exhaustion, while lactate levels remain relatively low. Acute quantitative ammonia production during intensive endurance exercise may be enhanced by a reduced glycogen availability in muscle. However, adequate amounts of glycogen itself do not prevent ammonia production when exercise is at high intensity and long-lasting.
<>The continuous ammonia accumulation in blood during endurance exercise in trained individuals may be the result of a relatively low blood flow to the liver and thereby low

clearance in contrast to lactate which may not accumulate due to a high clearance rate in both active and nonactive oxidative muscle fibers. In a number of subjects, it was observed that exhaustion, when performing endurance exercise at high exercise intensities, occurred when plasma ammonia levels were high. Muscle cramps occurred in subjects who reached their highest individual ammonia values and seemed not to be related to serum potassium, plasma lactate, or muscle glycogen. <>These individual observations give rise to the hypothesis that high intramuscular ammonia levels may be related to the etiology of muscle exhaustion and muscle cramping during highly intensive endurance exercise."[479.8]

[C] Caffeine decreases exercise and ketogenic diet-induced ammonia production.

"<>Objectives: Both exercise and a ketogenic (low-carbohydrate) diet favor glycogen depletion and increase ammonemia, which can impair physical performance. Caffeine supplementation has been routinely used to improve exercise performance. Herein, the effect of xanthine was evaluated on ammonemia in cyclists who were placed on a ketogenic diet and engaged in prolonged exercise.
<>Methods: Fourteen male cyclists followed a ketogenic diet for 2 d before and during the experimental trial. The cyclists were assigned to either the caffeine- (CEx; n = 7) or placebo-supplemented (LEx; n = 7) group. Blood samples were obtained during cycling and the recovery periods.
<>Results: The CEx group showed a significant decrease (up to 25%) in blood ammonia at 60, 90, and 120 min after beginning exercise compared with the LEx group. A higher concentration of apparent blood urea was observed in the LEx group than in the CEx group at 60 to 90 min of exercise (~10%). In addition, a significant increase in blood glucose levels was evident at 30 min of exercise (~28%), and an increase in blood lactate levels was visible during the first 30 to 60 min of exercise (~80%) in the CEx group.
<>Conclusions: Our results suggest that the consumption of caffeine might attenuate the increase in ammonemia that occurs during exercise."[479.9]

[D] Caloric Restriction (Carbohydrate Restriction) enhances Ammonia clearance through increasing the activity of the liver enzyme called Carbamyl phosphate synthetase I, which is essential to initiating the Urea Cycle[1]. This study is strange considering protein digestion is the primary cause of ammonia production, but explainable through a reduction in blood glucose[2].

[1] "<>Dietary calorie restriction (CR) delays age-related physiologic changes, increases maximum life span, and reduces cancer incidence. Here, we present the novel finding that chronic reduction of dietary calories by 50% without changing the intake of dietary protein induced the activity of mouse hepatic carbamyl phosphate synthetase I (CpsI) 5-fold. In liver, CpsI protein, mRNA, and gene transcription were each stimulated by

approximately 3-fold. Thus, CR increased both the rate of gene transcription and the specific activity of the enzyme. Short-term feeding studies demonstrated that higher cpsI expression was due to CR and not consumption of more dietary protein. Intestinal CpsI activity was stimulated 2-fold, while its mRNA level did not change, suggesting enzyme activity or translation efficiency was stimulated. CpsI catalyzes the conversion of metabolic ammonia to carbamyl phosphate, the rate-limiting step in urea biosynthesis. cpsI induction suggests there is a shift in the metabolism of calorie-restricted animals toward protein catabolism. CpsI induction likely facilitates metabolic detoxification of ammonia, a strong neurotoxin. Enhanced protein turnover and metabolic detoxification may extend life span. Physiologic similarities between calorie-restricted and hibernating animals suggest the effects of CR may be part of a spectrum of adaptive responses that include hibernation."

↓ Continued

[2] "<>Isocaloric diets containing 20% versus 4% protein increase hepatic cpsI precursor RNA and mRNA by ~3-fold in rats. In the study reported here, hepatic cpsI mRNA and gene transcription were induced ~3-fold by a 50% reduction of dietary calories without any change in dietary protein. In both kinds of studies, cpsI mRNA and gene transcription rates are high when calories derived from carbohydrates are low. Since it is not clear whether glucagon, insulin, or glucocorticoids are responsible for cpsI regulation in CR animals, it is possible that the gene responds directly to blood glucose concentrations. CR decreases blood glucose levels by 43% under the conditions used in this study."[479.10]

Other Hormones (Non-Androgenic)

As a preface, I feel it is necessary to remind you that many hormones accelerate the growth of cancers. Although it is my belief that *quality* of life is far more important than *length* of life, in this technological age, both parameters can be promoted simultaneously and efficiently. In our hypertoxic culture it is intelligent to treat all hormone deficiencies immediately, and adequately, for hormones are not only actuators of physical growth, but of mental growth. A deficiency in above all else, Thyroid Hormone, Testosterone, or Estrogen, is capable of derailing a person's life in youth through causing noticeable reductions in cognition.

Insulin

Forward: Insulins prime purpose is to promote the translocation of GLUT4 receptors, which are receptors that are contained within cells that move to the surface (translocate) to bind to ambient glucose molecules in the body and draw them into the cell for metabolism.

[A] Insulin is anabolic not only through activating the Akt Pathway, which activates mTORC1, but also through activating NF-kB and directly promoting inflammation. This is strange considering Protein Kinase B tends to reduces apoptosis in neurons, but there could be differential effects depending on concentration, timespan, and locality.

"<>In the present study, we have examined the insulin-signaling pathways involved in myogenesis in mouse C2C12 skeletal muscle cell line, a cellular system that expresses high number of high affinity insulin receptors. Insulin (50 nM) rapidly (5 min) stimulated beta-chain insulin receptor, activated the phosphatidylinositol (PI) 3-kinase/Akt/p70S6-kinase signaling pathway, as well as phosphorylated both p44/p42- and p38-mitogen-activated protein kinases (MAPKs). Preconfluent cells were differentiated in a serum-free medium in response to 50 nM insulin for 72 h, as revealed by the formation of multinucleated myotubes and the induction of the creatine kinase activity.
<>This differentiation process was also monitored by the inhibition of the PCNA content and induction of the cell cycle inhibitor p21. Furthermore, insulin induced nuclear factor-kappaB (NF-kappaB) DNA binding activity and down-regulated activating protein-1 (AP-1) DNA binding activity throughout the differentiation process. The use of specific inhibitors of the insulin-signaling pathways indicated that myogenesis was precluded by treatment for 72 h with LY294002 (an inhibitor of PI 3-kinase), rapamycin (a p70S6-kinase blocker), and SB203580 or PD169316 (p38-MAPK inhibitors). These inhibitors abolished insulin induction of NF-kappaB DNA binding activity and kappaB-chloramphenicol acetyltransferase (CAT) promoter activity, maintaining expressed cytosolic IkappaB-alpha protein, and increased AP-1 DNA binding activity and TRE-CAT promoter activity. These data suggest that insulin induces myogenesis in C2C12 through PI 3-kinase/ p70S6-kinase and p38-MAPK pathways, the signaling through p44/p42-MAPK being inhibited."[480]

[B] Insulin promotes memory formation through enhancing neuronal glucose uptake.

"<>The insulin-regulated glucose transporter, GluT4, is a key molecule in peripheral insulin signaling. Although GluT4 is abundantly expressed in neurons of specific brain regions such as the hippocampus, the functional role of neuronal GluT4 is unclear. Here, we used pharmacological inhibition of GluT4-mediated glucose uptake to determine whether GluT4 mediates insulin-mediated glucose uptake in the hippocampus. Consistent with previous reports, we found that glucose utilization increased in the dorsal hippocampus of male rats during spontaneous alternation (SA), a hippocampally-mediated spatial working memory task.
<>We previously showed that insulin signaling within the hippocampus is required for processing this task, and that administration of exogenous insulin enhances performance. At baseline levels of hippocampal insulin, inhibition of GluT4-mediated glucose uptake did not affect SA performance. However, inhibition of an upstream regulator of GluT4, Akt, did impair SA performance. Conversely, when a memory-enhancing dose of insulin

was delivered to the hippocampus prior to SA-testing, inhibition of GluT4-mediated glucose transport prevented cognitive enhancement. <>These data suggest that baseline hippocampal cognitive processing does not require functional hippocampal GluT4, but that cognitive enhancement by supra-baseline insulin does. Consistent with these findings, we found that in neuronal cell culture, insulin increases glucose utilization in a GluT4-dependent manner. Collectively, these data demonstrate a key role for GluT4 in transducing the procognitive effects of elevated hippocampal insulin."[481]

[C] Insulin promotes bDNF expression in young mice subjected to cognitive testing, which is why carbohydrates should rarely be restricted during childhood, but this effect is nullified in aged mice.

"<>Aging is a major risk factor for cognitive deficits and neurodegenerative disorders, and impaired brain insulin receptor (IR) signaling is mechanistically linked to these abnormalities. The main goal of this study was to investigate whether brain insulin infusions improve spatial memory in aged and young rats. Aged (24 months) and young (4 months) male Wistar rats were intracerebroventricularly injected with insulin (20 mU) or vehicle for five consecutive days. The animals were then assessed for spatial memory using a Morris water maze.
<>Insulin increased memory performance in young rats, but not in aged rats. Thus, we searched for cellular and molecular mechanisms that might account for this distinct memory response. In contrast with our expectation, insulin treatment increased the proliferative activity in aged rats, but not in young rats, implying that neurogenesis-related effects do not explain the lack of insulin effects on memory in aged rats. Furthermore, the expression levels of the IR and downstream signaling proteins such as GSK3-β, mTOR, and presynaptic protein synaptophysin were increased in aged rats in response to insulin.
<>Interestingly, insulin treatment increased the expression of the brain-derived neurotrophic factor (BDNF) and tropomyosin receptor kinase B (TrkB) receptors in the hippocampus of young rats, but not of aged rats. Our data therefore indicate that aged rats can have normal IR downstream protein expression but failed to mount a BDNF response after challenge in a spatial memory test. In contrast, young rats showed insulin-mediated TrkB/BDNF response, which paralleled with improved memory performance."[481.1]

Thyroid Hormone

[A] Triiodothyronine (T3) promotes MyoD expression. T3 is the biologically active downstream product of T4: Levothyroxine. Liothyronine (T3) is a prescription, and in those with simpler forms of hypothyroidism, not Hashimoto's disease, it may be more suitable for quickly counteracting the condition.

"<>We recently reported that triiodothyronine (T3) enhances MyoD gene expression and accelerates terminal differentiation in murine C2 myoblasts. In this paper, we are

interested in the effects of other hormones acting through related nuclear receptors. Retinoic acid (RA), but not estradiol or dexamethasone, is also able to enhance MyoD gene expression (about threefold). However, the effects of RA and T3 on myogenesis are quite distinct, with a much more potent RA action. Indeed, although T3 and RA positively regulate myogenesis with similar efficiency in poorly mitogenic conditions, in presence of high serum concentrations T3 can no longer trigger terminal differentiation whereas RA still remains efficient.
<>Thus, serum concentration is a crucial parameter in discriminating between the effects of T3 and RA on myogenesis. The differential effects between these two hormone are likely to be related to the ability of RA-activated endogenous retinoic acid receptors (RARs) to induce C2 myoblasts growth-arrest and to extinguish AP1 activity (thought to act as an inhibitor of myogenesis) whereas T3-activated endogenous thyroid hormones receptors (THRs) are relatively inefficient. We propose that the much higher level of RARs in C2 cells versus THRs could to some extent account for the differential ability of T3 and RA to antagonize serum-regulated mitogenic pathways in myogenic cells. This study provides clear evidence for an important role of RA on MyoD gene expression and myogenesis and suggests that T3 and RA could play overlapping, but distinct, roles on muscle development."[482]

[B] T3 promotes bDNF expression thus making thyroid hormone replacement therapy an essential part of healthy neurological aging, if the dosage of Levothyroxine or Liothyronine is sufficient.

"<>Thyroid hormones play important roles in the maturation and function of the central nervous system. However, the underlying mechanism behind thyroid hormone-regulated gene expression in the adult brain is not well understood. Two genes critical for neuronal plasticity and implicated in psychiatric disorders, reelin and brain-derived neurotrophic factor (BDNF), were investigated in the present study. Triiodothyronine (T3), the active form of thyroid hormone was administered to young adult rats in two different manners: systemic injection or local brain infusion.
<>Real time RT-PCR results revealed that T3 administration lead to a significant increase in reelin, total BDNF and exon-specific BDNF mRNA expression in the hippocampus. Furthermore, the association of transcriptional coactivators (including steroid receptor coactivator-1 (SRC-1), cAMP response element binding protein-binding protein (CBP), and thyroid hormone receptor associated protein 220 (TRAP 220)) and RNA polymerase II (RNA Pol II), with reelin and BDNF genes in the rat hippocampus displayed a distinct process following thyroid hormone administration. <>These findings suggest that association of transcriptional coactivators and RNA Pol II with gene promoters may be a possible mechanism explaining T3-induced reelin and BDNF expression in the hippocampus of young adult rats."[482.1]

[C] Thyroid Hormone (T3) is essential for skeletal muscle autophagy and skeletal muscle mitochondrial biogenesis through ROS-AMPK>PGC1a upregulation.

"<>Thyroid hormone (TH) and autophagy share similar functions in regulating skeletal muscle growth, regeneration, and differentiation. Although TH recently has been shown to increase autophagy in liver, the regulation and role of autophagy by this hormone in skeletal muscle is not known.
<>Here, using both in vitro and in vivo models, we demonstrated that TH induces autophagy in a dose- and time-dependent manner in skeletal muscle. TH induction of autophagy involved reactive oxygen species (ROS) stimulation of 5′adenosine monophosphate-activated protein kinase (AMPK)-Mammalian target of rapamycin (mTOR)- Unc-51-like kinase 1 (Ulk1) signaling. TH also increased mRNA and protein expression of key autophagy genes, microtubule-associated protein light chain 3 (LC3), Sequestosome 1 (p62), and Ulk1, as well as genes that modulated autophagy and Forkhead box O (FOXO) 1/3a.
<>TH increased mitochondrial protein synthesis and number as well as basal mitochondrial O2 consumption, ATP turnover, and maximal respiratory capacity. Surprisingly, mitochondrial activity and biogenesis were blunted when autophagy was blocked in muscle cells by Autophagy-related gene (Atg)5 short hairpin RNA (shRNA). Induction of ROS and 5′adenosine monophosphate-activated protein kinase (AMPK) by TH played a significant role in the up-regulation of Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PPARGC1A), the key regulator of mitochondrial synthesis.
<>In summary, our findings showed that TH-mediated autophagy was essential for stimulation of mitochondrial biogenesis and activity in skeletal muscle. Moreover, autophagy and mitochondrial biogenesis were coupled in skeletal muscle via TH induction of mitochondrial activity and ROS generation."[482.2]

[D] Levothyroxine at a dosage of ***1.6mcg per kg of bodyweight*** in aged mice was shown to not only mitigate cognitive deficits but enhance lifespan.

"<>The thyroid hormones, triiodothyronine and thyroxine, play important roles in cognitive function during the mammalian lifespan. However, thyroid hormones have not yet been used as a therapeutic agent for normal age-related cognitive deficits. In this study, CD-1 mice (aged 24 months) were intraperitoneally injected with levothyroxine (L-T4; 1.6 μg/kg per day) for 3 consecutive months.
<>Our findings revealed a significant improvement in hippocampal cytoskeletal rearrangement of actin and an increase in serum hormone levels of L-T4-treated aged mice. Furthermore, the survival rate of these mice dramatically increased from 60% to 93.3%. The Morris water maze task indicated that L-T4 restored impaired spatial memory in aged mice. Furthermore, level of choline acetyltransferase, acetylcholine, and superoxide dismutase were increased in these mice, thus suggesting that a possible

mechanism by which L-T4 reversed cognitive impairment was caused by increased activity of these markers. Overall, supplement of low-dosage L-T4 may be a potential therapeutic strategy for normal age-related cognitive deficits."[482.3]

Growth Hormone / IGF-1

Growth Hormone stimulates the production of IGF-1 in the liver. Although Life extension media will have you believe that the GH / IGF-1 axis accelerates ageing, this is just not the case. Growth Hormone Replacement Therapy (GHR) is likely to reduce lifespan through decreasing insulin sensitivity, which decreases AMPK, which decreases autophagy, which accelerates cellular senescence. Whereas decreasing endogenously produced GH, which already decreases steadily during aging, is not sufficient to cause a noticeable change in aging, and in fact, decreased GH in early childhood shortens lifespan[482.4].

GHR Therapy has numerous benefits on the brain, joints, muscles, and skin, and if quality of life matters more to you more than length of life, you should consider it.

I believe that the reason why many people prefer higher load resistance training over higher volume, lower load cardiovascular training is because traditional strength training promotes IGF-1 production in the muscles and liver[A], which diffuses into the bloodstream, passes the Blood Brain Barrier, and exerts neurotrophic effects of similar magnitude to bDNF, but these effects occur through enhanced myelination rather than neurogenesis, leading to enhanced neuronal stability (IGF-1 = + neuronal glucose uptake, + myelination, + axonogenesis = enhanced neuronal stress resilience / reduced behavioral flexibility), but not neuronal potential (bDNF = + neurogenesis, + synaptogenesis, + LTP = enhanced behavioral flexibility / enhanced anxiety). Therefore, cardiovascular exercise is for some anxiogenic (bDNF), whereas high load resistance training is anxiolytic (IGF-1), meaning that a balance in neuronal growth and neuronal maintenance can only be achieved through a balance of each exercise type, but it must be clarified that the increase in IGF-1 experienced from strength training will progressively decrease during aging, and we must remember that bDNF is a far greater brain fertilizer for the promotion of intelligence.

[A] "<>Neuroprotective factors are involved in brain functioning. Although physical exercise has been shown to have a positive influence on these factors, the effect of resistance exercise on them is not well known. This systematic review and meta-analysis aimed to 1) estimate the efficacy of resistance exercise on major neuroprotective factors, such as insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF), and vascular endothelial growth factor (VEGF), in middle and late life and 2) determine whether the effect is dose dependent.

<>A systematic search was conducted in CINAHL, Cochrane CENTRAL, MEDLINE, Scopus, PEDro, SPORTDiscus, and Web of Science up to November 2022. Random effects models were used to estimate standardized mean differences (SMDs) and their

respective 95% confidence intervals (CI) for the effect of resistance exercise on peripheral IGF-1, BDNF or VEGF levels in older adults.
<>Thirty randomized clinical trials with 1247 subjects (53.25% women, 45-92 years) were included in the systematic review, and 27 were selected for the meta-analysis. A significant effect of resistance exercise on IGF-1 levels was observed (SMD: 0.48; 95% CI: 0.27, 0.69), being more effective when performing 3 sessions/week (SMD: 0.55; 95% CI: 0.31, 0.79) but not on BDNF (SMD: 0.33; 95% CI: -0.29, 0.94). The effect on VEGF could not be determined due to the scarcity of studies.
<>Our data support the resistance training recommendation in middle and late life, at a frequency of at least 3 sessions/week, to mitigate the neurological and cognitive consequences associated with aging, mainly through IGF-1."[482.5]

[B] GH promotes the hypertrophy of newly formed (*nascent*) myofibers, which can then fuse with primary myotubes to form large myofibers i.e. GH is necessary for late stage hyperplasia.

"<>Growth hormone (GH) participates in the postnatal regulation of skeletal muscle growth, although the mechanism of action is unclear. Here we show that the mass of skeletal muscles lacking GH receptors is reduced because of a decrease in myofiber size with normal myofiber number. GH signaling controls the size of the differentiated myotubes in a cell-autonomous manner while having no effect on size, proliferation, and differentiation of the myoblast precursor cells. The GH hypertrophic action leads to an increased myonuclear number, indicating that GH facilitates fusion of myoblasts with nascent myotubes. NFATc2, a transcription factor regulating this phase of fusion, is required for GH action because GH is unable to induce hypertrophy of NFATc2-/- myotubes.
<>Finally, we provide three lines of evidence suggesting that GH facilitates cell fusion independent of insulin-like growth factor 1 (IGF-1) up-regulation. First, GH does not regulate IGF-1 expression in myotubes; second, GH action is not mediated by a secreted factor in conditioned medium; third, GH and IGF-1 hypertrophic effects are additive and rely on different signaling pathways. Taken together, these data unravel a specific function of GH in the control of cell fusion, an essential process for muscle growth."[483]

[C] IGF-1 promotes complete myogenesis.

"<>Skeletal myofibers differentiated from primary avian myoblasts in tissue culture can be maintained in positive nitrogen balance in a defined serum-free medium for at least 6-7 days when embedded in a three-dimensional collagen gel matrix. Incubation of established myofiber cultures for 3-7 days with insulin (1 microM) or insulin-like growth factor I (IGF-I, 32 nM) stimulates both cell hyperplasia and myofiber hypertrophy.

<>Mean myofiber diameter increases 71-98%. Insulin-like growth factor II stimulates cell hyperplasia but not myofiber hypertrophy. Cell growth results from a 42-62% increase in total protein synthesis and a 28-38% decrease in protein degradation. Myosin heavy-chain content increases 183-258% because of a 55% stimulation of myosin synthesis and 33-61% inhibition of degradation. Associated with myofiber hypertrophy is a 87-148% increase in the number of myofiber nuclei per unit myofiber length. <>The results indicate that insulin and IGF-I, but not IGF-II, can induce rapid myofiber hypertrophy in vitro, most likely by stimulating myoblast proliferation and/or fusion to established myofibers."[484]

[D] GH may cause insulin resistance in supraphysiological concentrations, thus explaining why many bodybuilders develop sickness in old age, an ironic homeostatic punishment for the ignorance of Substrate Competition.

"<>Growth hormone (GH) is a pleiotropic hormone that coordinates an array of physiological processes, including effects on bone, muscle, and fat, ultimately resulting in growth. Metabolically, GH promotes anabolic action in most tissues except adipose, where its catabolic action causes the breakdown of stored triglycerides into free fatty acids (FFA). GH antagonizes insulin action via various molecular pathways. Chronic GH secretion suppresses the anti-lipolytic action of insulin and increases FFA flux into the systemic circulation; thus, promoting lipotoxicity, which causes pathophysiological problems, including insulin resistance. In this review, we will provide an update on GH-stimulated adipose lipolysis and its consequences on insulin signaling in liver, skeletal muscle, and adipose tissue. Furthermore, we will discuss the mechanisms that contribute to the diabetogenic action of GH."[484.0]

Estrogen

This hormone strangely enough promotes myogenesis, especially in females, although the studies are contradictory, most likely due to a threshold effect. As your body fat increases your circulating estrogen increases because adipose tissue secretes Aromatase, that of which converts androgens into estrogens (estrone).

For women *approaching* the age of menopause, Estrogen Replacement Therapy (ERT) is equally as important as TRT is for men, for neurological, muscular, cardiovascular, and blood vessel health. I would suggest avoiding Oral Estrogens as they carry a higher risk of stroke, due to liver metabolism complications.

It must be mentioned that there currently is a wide scientific consensus on a "Critical Window" of ERT, wherein if therapy is not initiated speedily following menopause, it will serve no benefit to a woman's body or brain. The argument in favor of this Critical Window theory is the progressive degradation of estrogen receptors during aging, but this does not mean all of the estrogen receptors are degraded during aging, estrogen is still liable to exert many protective effects in females, even if administered late into life, as

many brain networks remain sensitive to estrogen [D]. Many gynecologists or primary care physicians will suggest that "estrogen has no systemic beneficial effects when administered long after menopause" but this is a foolish oversimplification. This disparity in hormone replacement therapy is evidence for a *sexism of ignorance* but not a *sexism of ill-intent* in considering elderly women are frequently provided no option for testosterone or estrogen replacement therapy, which makes aging gracefully much more difficult for them, in what regards their hearts, brains, and muscles. The self-administration of large dosages of DHEA, Alpha-GPC, and the use of potent phytoestrogens such as linalool are the only sensible options for an aged woman to delay her biological decay.

As an addendum for female readers: Ultra-Low Dose Testosterone Replacement Therapy is suggested by certain researchers and European Doctors for Post-Menopausal women, See [484.1], and I find it to be a superb idea, considering Testosterone is beneficial and necessary in both sexes.

[A] Estrone (a commonly prescribed derivative of estrogen) promotes myogenesis.

"<>To determine the role of estrogen in skeletal muscle growth, we investigated estrogen receptor-mediated effects on proliferation in skeletal myoblasts. In L6, C2C12 and Sol8 myoblasts estrogen receptor was demonstrated by immunoblotting, immunofluorescence microscopy and transfection studies. Estrone induced a significant increase in myoblast growth whereas 17 beta-estradiol had no effect. <>Furthermore, in L6-cells estrone (c-fos: 3.9-fold, egr-1: 4.6-fold) induced immediate-early gene induction significantly stronger than 17 beta-estradiol (c-fos: 1.7-fold, egr-1: 2.3-fold; $p < 0.05$). Skeletal myoblasts express functional estrogen receptors. Estrogens differ in the activation of skeletal myoblast growth and immediate-early gene induction."[485]

[B] The Estrogen Receptor responsible for estrogen's myogenic effects in both men and women is Estrogen Receptor Beta (ERβ).

"<>There is increasing evidence suggesting that estrogens augment skeletal muscle regeneration processes after injury. To study the contribution of estrogen receptors α and β (ERα and ERβ) during muscle regeneration, skeletal muscles of ovariectomized (OVX) rats, as well as ERα- and ERβ-knockout (αErko and βErko) mice, were injured with a myotoxin (notexin). OVX rats were simultaneously treated with the ER-selective ligands genistein, ERα agonist 16α-LE2 (alpha), ERβ agonist 8β-VE2 (beta), or 17β-estradiol (E(2)). OVX rats showed significantly elevated serum creatine kinase (CK) activity after muscle injury compared to intact sham-treated animals. Treatment with ER ligands significantly reduced CK activity. TNF-α, IL-10, and MCP-1 expression served to characterize immune responses. Treatment with all ER ligands, but particularly E(2) and beta, reduced TNF-α, but elevated MCP-1 and IL-10 expression. PCNA and MyoD expression served to define satellite cell activation and proliferation and were found to be up-regulated by beta and E(2).

<>To further study muscle regeneration responses, expression of the embryonic myosin heavy chain (MHC) was analyzed. Beta and E(2) but not alpha increased embryonic MHC expression compared to OVX. The absence of ERβ in βErko mice negatively affected CK activity levels and expression of satellite cell and muscle regeneration markers (MHC embryonic, MyoD, Pax7) compared with αErko and wild-type mice. In a classic Hershberger assay using male rats, beta stimulated muscle growth, accompanied by a strong induction of IGF-1 expression. Our data provide evidence that ERβ signaling is involved in the regulation of skeletal muscle growth and regeneration by stimulating anabolic pathways, activating satellite cells and modulating immune responses."[485.1]

[C] Transdermal Estrogen Replacement Therapy promotes bDNF expression in post-Menopausal female athletes.

"<>Amenorrhea and osteoporosis are strongly associated in female athletes. Amenorrheic women show lower serum levels of brain-derived neurotrophic factor (BDNF) than eumenorrheic women. BDNF is known to regulate bone tissue development and remodeling; thus, athletes with low serum BDNF levels may show low bone mass.
<>This study investigated the associations between serum BDNF, estradiol, and bone mineral density (BMD) in female athletes. This study included 160 elite female athletes (21.7±4.3 years). Serum levels of BDNF and estradiol were in 195 blood samples obtained from 132 eumenorrheic athletes (EA) and 63 amenorrheic athletes (AA). BMD was measured in the radius, lumbar spine, pelvis, and legs using dual-energy X-ray absorptiometry.
<>AA showed significantly lower serum BDNF levels than EA ($p=0.017$). Serum BDNF levels were positively and significantly associated with both serum estradiol levels ($p=0.0004$) and the BMD measured at all sites (all $p<0.05$). 10 AA received transdermal estrogen therapy, and serum BDNF levels were measured at baseline and 6 months after therapy.
<>Hormone-treated AA demonstrated a significant increase in serum BDNF levels after 6 months ($p=0.022$). Thus, serum BDNF levels may be associated with decreased BMD and serve as an indicator of the therapeutic effect of estradiol supplementation in female athletes with osteoporosis."[485.2]

[D] The Arcuate Nucleus, and the genes Pomc (see: Fasting), Npy, & Hcrt are still highly sensitive to Estrogen replacement, even after menopause, challenging this dangerous "Critical Window Theory". This means ERT even in older women is still liable to beneficially change several health factors such as Appetite, Weight, Arousal, Thermoregulation, & even their Circadian Rhythm. (See full free form research article for visual representations)

"<>Our study systematically evaluated the effects of age, in conjunction with timing and duration of E2 treatment, on the dynamics of hypothalamic gene expression patterns in

relation to physiological and hormonal responses. Overall, our results showed that E2 status was by far the dominant factor determining outcomes, with age, timing, and duration playing secondary roles. This result is of fundamental importance given the ongoing debates about E2 replacement therapy. Moreover, analysis of coexpression gene modules allowed us to gain detailed insights into groups of genes in 2 key hypothalamic regions that are correlated in their expression and responses to the experimental manipulations. Gene and hormone analyses also identified several significant effects of age, timing, and duration of hormone that may be relevant to the physiological effects of E2 on neuroendocrine functions.

<>Gene expression in the ARC is highly E2-responsive and includes kisspeptin-neurokinin B-prodynorphin (KNDy) neurons. We designed our PCR card to include genes in the hypothalamus involved in energy balance, circadian regulation, reproduction, neurotransmitter and hormone signaling. Our analysis identified several gene coexpression modules for which E2 treatment was the dominant factor driving the clustering. Only 1 module (blue) was up-regulated by E2 treatment. Three modules showed down-regulation in response to E2 with secondary effects of timing and trends for duration. The brown module was of particular interest as its genes were strongly down-regulated by E2 regardless of the timing and duration. This module comprised genes that include the estrogen receptor (ER)α (Esr1), KNDy signaling (Kiss1 and Tac2), energy and electrolyte balance (Pomc and Avpr1a), melatonin responsiveness (Mtnr1b), and neuronal differentiation (Nkx2.1). KNDy neurons in the ARC coexpress Esr1 and are a central node in the control of GnRH secretion. KNDy neurons are sexually dimorphic, hormone-responsive, and are critically involved both in reproductive function and energy balance.

<>As shown previously, the population of KNDy neurons in the ARC exhibits E2- and age-related morphological changes such as neuronal hypertrophy and cell loss. It is established that hypothalamic Kiss1 and Tac2 are elevated in parallel with diminished serum E2 and increased GnRH/LH release in postmenopausal women, macaques, and OVX rodents. Our gene coexpression analysis provides a unique way to examine the KNDy pathway in a manner that provides insights to several important neuroendocrine systems. Consistent with previous reports, expression of kisspeptin (Kiss1) and neurokinin-B (Tac2) in our rats' ARC brown module was strongly down-regulated by E2 treatment. In the red module, prodynorphin (Pdyn) was down-regulated by E2 with a trend in the duration analysis. This agrees with other studies showing differences in the gene expression pattern between Pdyn with Kiss1 and Tac2 and adds in the age and duration analysis. The differential clustering of Pdyn and Kiss1/Tac2 might also be related to changes of non-KNDy prodynorphin neurons and neurokinin-B neurons in the ARC.

<>The receptor targets of KNDy neurons have mainly been studied on the regulation of GnRH neurons and reproductive function. In our study, gene expression of kisspeptin receptor (Kiss1r) in the yellow module was not as robustly down-regulated by E2 as its

corresponding ligand, Kiss1, in the brown module. The neurokinin B receptor (Tacr3) was in the green module, which was the only module not affected by age and/or E2 in the ARC.
<>Our data agree with the suggestion that the modulation of KNDy ligand-receptor pathways in the ARC (and median eminence) is mediated primarily through ligand synthesis rather than receptor modulation. Furthermore, these data show differential effects of age and duration of E2 but no effects of timing."[485.2.1]

[E] Estrogen promotes NMDAr activity in the CA1 subfield of the hippocampus to promote working memory performance, and this effect can be mimicked in either sex through boosting neurological Acetylcholine levels (See: Alpha-GPC).

"<>Elevated levels of circulating estrogen in female rats result in increased spine and synapse density and parallel increases in NMDA receptor binding in area CA1 of the hippocampus. Estrogen also influences cholinergic neurochemistry in the basal forebrain and hippocampus.
<>The objectives of the present study were to determine the role of acetylcholine in the estrogen-induced increase in NMDA receptor binding in CA1 of the hippocampus and to investigate the relationship between increased NMDA receptor binding in CA1 and performance on a task of working memory. In the current experiments, elevating endogenous levels of acetylcholine in ovariectomized rats by 3 d of continuous administration of physostigmine, an acetylcholinesterase inhibitor, increased NMDA receptor binding in CA1 as measured by quantitative autoradiography. This increase was comparable with the increase in NMDA receptor binding induced by injections of estradiol benzoate 72 and 48 hr before death.
<>Additionally, the administration of 5,11-dihydro-8-chloro-11-[[4-[3-[(2,2-dimethyl-1-oxopentyl)ethylamino]propyl]-1-piperidinyl]acetyl]-6H-pyrido[2,3-b][1,4]benzodiazepin-6-one (BIBN 99), an M2 receptor antagonist, blocked the ability of both estrogen and physostigmine to increase NMDA receptor binding. The regimen of estradiol replacement that was demonstrated to increase NMDA receptor binding in CA1 of ovariectomized rats also improved arm-choice accuracy in a working memory task in an eight-arm radial maze. The estrogen-induced improvement in working memory performance was blocked by BIBN 99, which also blocked the increase in NMDA receptor binding.
<>These results indicate that acetylcholine acts at M2 muscarinic receptors to mediate the estrogen-induced increase in NMDA receptor binding in CA1 of the hippocampus as well as the associated improvement in working memory."[485.2.2]

Cortisol

Cortisol is a steroid hormone and the primary glucocorticoid that regulates blood sugar,

exerts immunosuppressive effects, and causes proteolysis. The general two purposes of this hormone are to provide the body with the glucose necessary for survival during physiological stress by mobilizing fatty acids and breaking down muscle tissue, and by increasing memory consolidation of emotionally negative stimuli but decreasing memory consolidation of neutral stimuli, thereby facilitating a cognitive state necessary for survivalism.

Cortisol is deactivated when our body converts it to cortisone through kidney enzymatic processes, and cortisone is re-converted into cortisol in our liver.

[A] High levels of Cortisol reduce lipolysis in the trunk (abdominal area), while promoting lipolysis in other regions of the body.

"<>Cortisol is known to increase whole body lipolysis, yet chronic hypercortisolemia results in increased fat mass. The main aim of the study was to explain these two apparently opposed observations by examining the acute effects of hypercortisolemia on lipolysis in subcutaneous adipose tissue and in the whole body.
<>Six healthy subjects were studied on two occasions. On one occasion hydrocortisone sodium succinate was infused i.v. to induce hypercortisolemia (mean plasma cortisol concentrations, 1500 +/- 100 vs. 335 +/- 25 nmol/L; $P < 0.001$); on the other occasion (control study) no intervention was made. Lipolysis in the s.c. adipose tissue of the anterior abdominal wall was studied by measurement of arterio-venous differences, and lipolysis in the whole body was studied by constant infusion of [1,2,3-2H5]glycerol for measurement of the systemic glycerol appearance rate. <>Hypercortisolemia led to significantly increased arterialized plasma nonesterified fatty acid (NEFA; $P < 0.01$) and blood glycerol concentrations ($P < 0.05$), with an increase in systemic glycerol appearance ($P < 0.05$). However, in s.c. abdominal adipose tissue, hypercortisolemia decreased veno-arterialized differences for NEFA ($P < 0.05$) and reduced NEFA efflux ($P < 0.05$). This reduction was attributable to decreased intracellular lipolysis ($P < 0.05$), reflecting decreased hormone-sensitive lipase action in this adipose depot.
<>Hypercortisolemia caused a reduction in arterialized plasma TAG concentrations ($P < 0.05$), but without a significant change in the local extraction of TAG (presumed to reflect the action of adipose tissue lipoprotein lipase). There was no significant difference in plasma insulin concentrations between the control and hypercortisolemia study. Site-specific regulation of the enzymes of intracellular lipolysis (hormone-sensitive lipase) and intravascular lipolysis (lipoprotein lipase) may explain the ability of acute cortisol treatment to increase systemic glycerol and NEFA appearance rates while chronically promoting net central fat deposition."[485.3]

[A2] Larger secretions of Cortisol during stress are positively associated with high abdominal fat mass (waist-to-hip ratio).

“<>Recent studies have shown an association between uncontrollable stress and abdominal fat distribution. It has been suggested that changes in cortisol secretion might represent one possible mechanism for this relationship. This study investigated whether body fat distribution, determined by waist-to-hip ratio (WHR), is related to salivary cortisol levels in response to laboratory stressors. Subjects were 41 overweight women with a Low or a High WHR. Multiple measures of cortisol and mood were obtained during a session of stressful tasks (eg., timed arithmetic) and during a time-matched, control rest session.
<>Also, background life stress and psychological trait variables were assessed. Compared to Low WHR subjects, High WHR subjects secreted significantly more cortisol during the stressful session after 60 minutes of stress, and considering the total area under the curve of secretion. This difference was not seen on the rest day. In terms of background and psychological measures, High WHR subjects were characterized by poorer coping skills and differences in mood reactivity. Specifically, although all subjects became more angry in response to the stressful session, High WHR subjects showed smaller increases in anger.
<>This could indicate that they are more likely to evidence a helpless reaction to uncontrollable stress. These findings support the hypothesis that cortisol secretion might represent a mechanism for the observed association between stress and abdominal fat distribution. Furthermore, differences in coping and appraisal may suggest that a particular psychological pattern might influence the reactivity of the adrenal-cortical system to stress, and subsequent fat distribution.”[485.4]

[B] Only extremely high levels (supraphysiological) of Cortisol are capable of burning fat chronically, and only in the presence of Adrenaline or Insulin.

“<>In vivo, high cortisol increased lipolysis only in the presence of high insulin and/or adrenaline but did not alter glucose kinetics. High cortisol increased adipose mRNA levels of ATGL, HSL and CGI-58 and suppressed G0S2. In vitro, high cortisol increased lipolysis in the presence of insulin in subcutaneous, but not visceral, adipocytes.
<>The acute lipolytic effects of cortisol require supraphysiological concentrations, are dependent on insulin and adrenaline and are observed only in subcutaneous adipose tissue. The resistance of visceral adipose tissue to cortisol's lipolytic effects may contribute to the central fat accumulation observed with chronic glucocorticoid excess.”[485.5]

[C] Cortisol is a neurotoxin, especially in developing brains, as prenatal dexamethasone (a chemical 30x more potent than cortisol) causes a permanent upregulation in cortisol production.

"<>Severe and prolonged physical and psychological stress is known to cause brain damage; long-term torture victims in prison have later developed psychiatric disorders and cerebral cortical atrophy observed in CT scans. In nonhuman primates, we observed degeneration and depletion of the hippocampal neurons in African green monkeys that had been severely abused by cagemates and died with complications of multiple gastric ulcers and adrenal cortical hyperplasia.
<>In our previous studies the administration of dexamethasone (DEX) (5 mg/kg) to pregnant rhesus monkeys at 132 to 133 days of gestation induced degeneration and depletion of the hippocampal pyramidal and dentate granular neurons in the brains of 135-gestation-day fetuses, and these changes were retained in the brains of fetuses at near term, 165 days of gestation. We also found that implantation of a cortisol pellet in the vicinity of the hippocampus in adult vervet monkeys induced degeneration of the CA3 pyramidal neurons and their dendritic branches. Thus, hippocampal pyramidal neurons containing a high concentration of glucocorticoid receptors appear to be highly vulnerable to either hypercortisolemia caused by severe stress or to exposure to exogenous glucocorticoids.
<>To study the long-term postnatal sequelae of prenatal brain damage, eight rhesus monkeys were treated with either DEX (5 mg/kg), 5 animals, or vehicle, 3 animals, at 132 to 133 days of gestation. After natural birth, all animals lived with their mothers for 1 year. At 9 months of age, we found that DEX-treated animals had significantly high plasma cortisol at both base and post-stress (isolation) levels compared to age-matched vehicle-treated animals.
Magnetic resonance images (MRI) of the brain at 20 months of age showed an approximately 30% reduction in size and segmental volumes of the hippocampus in DEX-treated compared to vehicle-treated animals. Measurements of whole brain volume by MRI showed no significant differences between DEX and vehicle groups. Prenatal administration of a potent glucocorticoid (DEX) induced an irreversible deficiency of the hippocampal neurons and high plasma cortisol at the circadian baseline and post-stress levels in juvenile rhesus monkeys. These results suggest that the hippocampus mediates negative feedback of cortisol release; a lack or deficiency of the hippocampal neurons attenuates this feedback resulting in hypercortisolemia."[485.6]

[D] The primary purpose of cortisol release following psychological stress is to enhance negatively charged (threatening, sad, etc.) emotional memory consolidation, thereby promoting our survival as a species by increasing the strength of negative memories.

"<>Emotional experiences create durable memory traces in the brain, especially when these memories are consolidated in the presence of stress hormones such as cortisol. Although some research suggests cortisol elevation can increase long-term memory for emotional relative to neutral content, the impact of stress and cortisol on the

consolidation of emotional and neutral aspects of memories when they are part of the same experience remains unknown.
<>Here, after encoding complex scenes consisting of negative or neutral objects placed on neutral backgrounds, participants were exposed to a psychosocial stressor (or matched control condition) in order to examine the impact of stress and cortisol on early consolidation processes. The next day, once cortisol levels had returned to baseline, specific and gist recognition memory were tested separately for objects and backgrounds.
<>Results indicate that while there was a numerical increase in memory for negative objects in the stress group, higher endogenous cortisol concentrations were specifically associated with decreased memory for the neutral backgrounds originally paired with negative objects. Moreover, across all participants, cortisol levels were positively correlated with the magnitude of the emotional memory trade-off effect. Specifically, while memory for negative objects was preserved, elevated cortisol during early consolidation was associated with decreased memory for neutral backgrounds that were initially paired with negative objects. These memory effects were observed in both the stricter specific measure of memory and the less conservative measure of gist memory.
<>Together, these findings suggest that rather than influencing all aspects of an experience similarly, elevated cortisol during early consolidation selectively preserves what is most emotionally salient and adaptive to remember while allowing the loss of memory for less important neutral information over time."[485.7]

[E] Higher intensity exercise, as expected, enhances cortisol release. But interestingly, lower intensity exercise at 40% VO2 Max (115-120BPM for the average gym goer) results in lower average cortisol levels post-exercise, likely related to increased immune strength following lower intensity exercise sessions.

"<>This study examined the influence of exercise intensity upon the cortisol response of the hypothalamic-pituitary-adrenal (HPA) axis. Specifically, we examined exercise at intensities of 40, 60, and 80% maximal oxygen uptake (VO2max) in an attempt to determine the intensity necessary to provoke an increase in circulating cortisol.
<>Twelve active moderately trained men performed 30 min of exercise at intensities of 40, 60, and 80% of their VO2max, as well as a 30-min resting-control session involving no exercise on separate days. Confounding factors such as time of day--circadian rhythms, prior diet--activity patterns, psychological stress, and levels of exercise training were controlled. Cortisol and ACTH were assessed in blood collected immediately before (pre-) and after (post-) each experimental session. Statistical analysis involved repeated measures analysis of variance and Tukey post-hoc testing.
<>The percent change in cortisol from pre- to post-sampling at each session was: resting-control, 40, 60, and 80% sessions (mean+/-SD) =-6.6+/-3.5%, +5.7+/-11.0%, +39.9+/-11.8%, and +83.1+/-18.5%, respectively. The 60% and 80% intensity magnitude of change was significantly greater than in the other sessions, as well as from one to

another. The ACTH responses mirrored those of cortisol, but only the 80% exercise provoked a significant ($p<0.05$) increase pre- to post-exercise. The calculated changes in plasma volume for the resting-control, 40%, 60%, and 80% sessions were: +2.2+/-3.0%, -9.9+/-5.0%, -15.6+/-3.5%, and -17.2+/-3.3%, respectively. Collectively, the cortisol findings support the view that moderate to high intensity exercise provokes increases in circulating cortisol levels.
<>These increases seem due to a combination of hemoconcentration and HPA axis stimulus (ACTH). In contrast, low intensity exercise (40%) does not result in significant increases in cortisol levels, but, once corrections for plasma volume reduction occurred and circadian factors were examined, low intensity exercise actually resulted in a reduction in circulating cortisol levels."[485.8]

[E2] Cortisol release in response to Psychological stress is blunted following high intensity exercise, proving that although strenuous exercise enhances cortisol release, it protects the brain from psychological stress.

"<>Objective: The aim of this experimental study was to determine the extent to which the intensity of a single 30 min bout of exercise alters the salivary cortisol (sCort) response to a subsequently induced acute psychosocial stressor. The study further aimed to elucidate a physiological mechanism through which exercise intensity exerts stress-mitigating effects.
<>Methods: Eighty-three healthy men (Mage = 21.04 SD = 2.89) were randomly assigned to exercise on a treadmill at either 30%, 50% or 70% of their heart rate reserve (HRR) for 30 min and then underwent the Trier Social Stress Test 45 min later. sCort was measured repeatedly throughout and following the exercise bout and stressor task.
<>Results: ANCOVA and Multilevel Growth Curve Analysis determined that vigorous (70% HRR) exercise elicited dampened sCort responses to the stressor task, marked by lower total sCort levels, diminished sCort reactivity, and faster recovery to baseline values, as compared to less intense exercise. Moreover, exercise elicited a sCort response in proportion to the intensity at which it was performed, and this exercise-associated HPA-axis response was inversely proportional to the sCort response to the subsequent stressor task.
<>Conclusions: This study revealed that exercise-intensity dampens the HPA-axis stress response in a dose-dependent manner, with evidence that the cortisol released from exercising intensely suppresses the subsequent cortisol response to a psychosocial stressor."[485.9]

[F] The Glucocorticoid receptor may be partially necessary for the activation of REDD1 following aerobic exercise, and the resultant post-exercise genetic changes in skeletal muscle such as those relating to protein synthesis, metabolism, and neuromuscular

junction remodeling. In this study mice engaged in a moderate-intensity treadmill running exercise protocol.

"<>The metabolic stress placed on skeletal muscle by aerobic exercise promotes acute and long-term health benefits in part through changes in gene expression. However, the transducers that mediate altered gene expression signatures have not been completely elucidated. Regulated in development and DNA damage 1 (REDD1) is a stress-induced protein whose expression is transiently increased in skeletal muscle following acute aerobic exercise. However, the role of this induction remains unclear. Because REDD1 altered gene expression in other model systems, we sought to determine whether REDD1 induction following acute exercise altered the gene expression signature in muscle.
<>To do this, wild-type and REDD1-null mice were randomized to remain sedentary or undergo a bout of acute treadmill exercise. Exercised mice recovered for 1, 3, or 6 h before euthanization. Acute exercise induced a transient increase in REDD1 protein expression within the plantaris only at 1 h postexercise, and the induction occurred in both cytosolic and nuclear fractions. At this time point, global changes in gene expression were surveyed using microarray. REDD1 induction was required for the exercise-induced change in expression of 24 genes. Validation by RT-PCR confirmed that the exercise-mediated changes in genes related to exercise capacity, muscle protein metabolism, neuromuscular junction remodeling, and Metformin action were negated in REDD1-null mice.
<>Finally, the exercise-mediated induction of REDD1 was partially dependent upon glucocorticoid receptor activation. In all, these data show that REDD1 induction regulates the exercise-mediated change in a distinct set of genes within skeletal muscle.[485.10]

[F2] REDD1 appears to suppress mTORC1 and associate predominately with the slow twitch phenotype [See: Common Recreation Chemicals: Alcohol]

"<>Working muscle conserves adenosine triphosphate (ATP) for muscle contraction by attenuating protein synthesis through several different pathways. Regulated in development and DNA damage response 1 (REDD1) is one candidate protein that can itself attenuate muscle protein synthesis during muscle contraction. In this study, we investigated whether endurance exercise induces REDD1 expression in association with decreased mammalian target of rapamycin (mTOR) complex I (mTORC1) signaling and global protein synthesis in rat skeletal muscle. After overnight fasting, rats ran on a treadmill at a speed of 28 m/min for 60 min, and were killed before and immediately, 1, 3, 6, 12, and 24 h after exercise.
<>REDD1 mRNA and corresponding protein levels increased rapidly immediately after exercise, and gradually decreased back to the basal level over a period of 6 h in the gastrocnemius muscle. Phosphorylation of mTOR Ser2448 and S6K1 Thr389 increased

with the exercise, but diminished in 1–3 h into the recovery period after cessation of exercise. The rate of protein synthesis, as determined by the surface sensing of translation (SUnSET) method, was not altered by exercise in fasted muscle.
<>These results suggest that REDD1 attenuates exercise-induced mTORC1 signaling. This may be one mechanism responsible for blunting muscle protein synthesis during exercise and in the early postexercise recovery period."[485.11]

Extreme Tempo Superslow Training

Having experimented with Superslow Eccentric Strength (SES) Training and Superslow Concentric Strength (SCS) Training for many years, I am certain they hold a greater anabolic reward compared to regular-speed training and the research has confirmed this. For simplicity, I classify combing SES with SCS as "*Extreme* Tempo: Superslow Training", or **ET:SS** for short when both phases of the lift (concentric and eccentric) are between 8-12 seconds of stable, controlled tension, and higher loads are lifted, requiring great mental exertion.

Although workouts can be performed with a focus on eccentricity or concentricity alone, combing them is a simpler way to train, but with greater muscular breakdown comes a greater need for recovery. If you engage in ET:SS, hypertrophy will be delayed post-workout beyond the classically recommended 72h rest period, and over the 96h IMC recommended rest period, to at or near 120h, so too will your tendons be heavily damaged, therefore do not experiment with ET:SS training without giving your body an adequate recovery period of between seven or more days between another ET:SS or regular-speed higher load session, or you will injure yourself. Although not training a muscle for 120h may result in a very small amount of Vascular Deconditioning occurring, it is worth it to allow the muscles a complete recovery from detraining. A limit of once per week high load ET:SS is suggested.

It's safe to suggest that Superslow Eccentric Training is more damaging to fast twitch muscle fibers, whereas Superslow Concentric Training is more damaging to slow twitch fibers, depending on the loads, as obviously with max loads all muscle fibers become activated, but with lower to moderate loads, an isolative effect on muscle fiber recruitment is liable to occur in my opinion.

Regarding Speedwork: Extreme Tempo Superfast Training (Explosive Training)

Olympic Lifters have proven for a great number of years that explosive lifting (speedwork), and high frequency training are capable of promoting great increases in absolute strength, but they also have proven that overtraining is real, regardless of drug use. For why else would an athlete stop lifting weights, except for injury, even off-cycle? Retirement too does not make one lose their passion for exercise. It is my opinion that Superfast Training should trained once per month in the form of low load, high volume

(20-60 Repetition sets) isolation work with resistance bands, or with a Partial ROM (50%) exercise and very light barbell. The key points being “low load” + “high volume”, as there’s no reason to risk injury with explosive lifting, when Eccentric Superslow strength training will build fast twitch fibers more efficiently.

It’s clear that Compensatory Acceleration Training with high loads enhances absolute power through growing fast twitch fibers, but it is not a viable training method for long term goals, it is absolutely not sustainable, and in a natural athlete it will cause an injury at some point.

[1] Eccentric Exercise damages muscle tissue to a greater extent than concentric because of sarcomere lengthening (muscle damage), and more than likely because of greater muscle fiber *peeling*. This does not mean concentric exercise does not damage muscle tissue similarly, but the damaging effects of each contraction type are different because eccentric contraction causes far greater mechanical tension in muscle tissue leading to greater breakdown in myofibrils, which stimulates greater post-exercise adaptations through increased Cytokine and MRF production. There is no doubt that if Eccentric Exercise is performed with high loads, high volume, and at a high frequency, muscle tissue may be damaged beyond the body’s ability to repair it (hypertrophy potential), eventually leading to muscle fibrosis, or severe muscle atrophy, therefore a detraining period of 96-Hours is mandatory after any strenuous eccentric exercise. Furthermore, from training experience and all of the research on inflammation listed before this point, the use of antioxidants or anti-inflammatory compounds in the hours or days after strenuous eccentric exercise is liable in my opinion to halt muscle hypertrophy, as pro-inflammatory factors obviously serve the express purpose of facilitating early wound healing, and to halt this physiological response is to perturb muscle growth.

“<>In eccentric exercise the contracting muscle is forcibly lengthened; in concentric exercise it shortens. While concentric contractions initiate movements, eccentric contractions slow or stop them. A unique feature of eccentric exercise is that untrained subjects become stiff and sore the day afterwards because of damage to muscle fibres. This review considers two possible initial events as responsible for the subsequent damage, damage to the excitation-contraction coupling system and disruption at the level of the sarcomeres. Other changes seen after eccentric exercise, a fall in active tension, shift in optimum length for active tension, and rise in passive tension, are seen, on balance, to favour sarcomere disruption as the starting point for the damage. As well as damage to muscle fibres there is evidence of disturbance of muscle sense organs and of proprioception.

<>A second period of exercise, a week after the first, produces much less damage. This is the result of an adaptation process. One proposed mechanism for the adaptation is an increase in sarcomere number in muscle fibres. This leads to a secondary shift in the muscle's optimum length for active tension. The ability of muscle to rapidly adapt following the damage from eccentric exercise raises the possibility of clinical

applications of mild eccentric exercise, such as for protecting a muscle against more major injuries."[485.12]

[A] Eccentric Exercise facilitates predominately fast twitch fiber growth.

"<>Introduction: Satellite cells (SCs) are of key importance in skeletal muscle tissue growth, repair, and regeneration. A single bout of high-force eccentric exercise has been demonstrated to increase mixed muscle SC content after 1-7 d of postexercise recovery. However, little is known about fiber type-specific changes in SC content and their activation status within 24 h of postexercise recovery.
<>Methods: Nine recreationally active young men (23 ± 1 yr) performed 300 eccentric actions of the knee extensors on an isokinetic dynamometer. Skeletal muscle biopsies from the vastus lateralis were collected preexercise and 24 h postexercise. Muscle fiber type-specific SC content and the number of activated SCs were determined by immunohistochemical analyses.
<>Results: There was no difference between Type I and Type II muscle fiber SC content before exercise. SC content significantly increased 24 h postexercise in Type II muscle fibers (from 0.085 ± 0.012 to 0.133 ± 0.016 SCs per fiber, respectively; $P < 0.05$), whereas there was no change in Type I fibers. In accordance, activation status increased from preexercise to 24 h postexercise as demonstrated by the increase in the number of DLK1+ SCs in Type II muscle fibers (from 0.027 ± 0.008 to 0.070 ± 0.017 SCs per muscle fiber $P < 0.05$). Although no significant changes were observed in the number of Ki-67+ SCs, we did observe an increase in the number of proliferating cell nuclear antigen-positive SCs after 24 h of postexercise recovery.
<>Conclusion: A single bout of high-force eccentric exercise increases muscle fiber SC content and activation status in Type II but not Type I muscle fibers."[486]

[A2] Eccentric Exercise facilitates fast twitch fiber growth by way of Toll Like Receptor 4. [See: Pro-Inflammation Cycle Dietary Fats: Lauric Acid]

"<>This study aimed to investigate the response of the toll-like receptor 4 (TLR4) signaling pathway to an acute bout of eccentric exercise, and to assess whether eccentric training attenuated the effects induced by acute eccentric exercise. Twenty men (22.4 ± 0.5 yr) were divided into a control group (CG, n = 8) and a training group (TG, n = 12). Both groups performed two acute eccentric bouts on a squat machine in a 9-wk interval. During this time, TG followed a 6-wk eccentric training program (3 session/wk; 3-5 sets of 10 repetitions with loads ranging between the 40 and 50% of maximal isometric voluntary contraction). CD14, TLR4, and TNF-α mRNA levels, and CD14, TLR4, myeloid differentiation factor 88, tumor necrosis factor receptor-associated factor 6, TIR-domain-containing adapter-inducing interferon-β, phospho-IκB kinases, phospho-IκB, phospho-ERK-1/2, and TNF-α protein concentration were measured in peripheral blood mononuclear cells, before, immediately, and 2 h after each eccentric bout.

<>The first acute eccentric bout triggered a proinflammatory response mediated by an upregulation of all of the factors measured within the TLR4 signaling pathway. Following the training period and after the second acute bout, CG showed a similar proinflammatory response than that seen after the first bout. However, the eccentric training intervention decreased significantly the protein concentration of all factors analyzed in TG compared with results obtained after the first bout. These results suggest that the TLR4-signaling pathway plays a critical role in the proinflammatory response seen after acute eccentric exercise. This response was attenuated after an eccentric training program through myeloid differentiation factor 88-dependent and -independent pathways."[487]

[A3] Eccentric exercise decreases myostatin expression.

"<>Evidence indicates that repeated-bouts of eccentric exercise (EE) do not exacerbate the extent of muscle damage indices, as compared to a single-bout. We hypothesized that molecular adaptations, under repeated-bouts of EE, would include suppression of muscle repair inhibitory factors such as myostatin and up-regulation of muscle repair positive regulatory factors such as myogenic regulatory factors (MRFs). Fifteen males were recruited for this study. The exercise group (n=9) successfully completed six sets of 15 reps of maximum voluntary eccentric contractions, for six consecutive days, using a dynamometer (Multicont-II). Blood and muscle biopsy samples were obtained from each subject 1 week prior to exercise, 2 days post the first training session, and 24 h after the last training session. Gene expression levels were determined using real-time RT-PCR. Blood samples were analyzed for creatine kinase (CK) and lactate-dehydrogenase (LDH) activity.
<>Repeated-bouts of EE induced a large down-regulation of myostatin mRNA (-73%) which persisted throughout the study. The responses of MRFs were mild. At day 3 only myogenin increased significantly (1.9 fold) while MyoD decreased by 45%. Surprisingly, at day 7, despite the presence of muscle damage indices, all MRFs returned to the pre-exercise levels. The results of the present study showed that repeated-bouts of EE, for six consecutive days, dramatically decreased Myostatin mRNA expression but impaired the expression patterns of MRFs such that, with the exception of myogenin that showed a moderate non-sustained increase, MyoD and MYf5 response was minimal."[488]

[A4] Eccentric exercise reduces muscle atrophy factors.

"<>Resistance training using lengthening (eccentric) contractions induces greater increases in muscle size than shortening (concentric) contractions, but the underlying molecular mechanisms are not clear. Using temporal expression profiling, we compared changes in gene expression within 24 h of an acute bout of each type of contractions conducted simultaneously in the quadriceps of different legs. Five healthy young men performed shortening contractions with one leg while the contralateral leg performed lengthening contractions. Biopsies were taken from both legs before exercise and 3, 6,

and 24 h afterwards, in the fed state. Expression profiling (n = 3) was performed using a custom-made Affymetrix MuscleChip containing probe sets of approximately 3,300 known genes and expressed sequence tags expressed in skeletal muscle.
<>We identified 51 transcripts differentially regulated between the two exercise modes. Using unsupervised hierarchical clustering, we identified four distinct clusters, three of which corresponded to unique functional categories (protein synthesis, stress response/early growth, and sarcolemmal structure). Using quantitative RT-PCR (n = 5), we verified expression changes (lengthening/shortening) in SIX1 (3 h, -1.9-fold, $P < 0.001$), CSRP3 (6 h, 2.9-fold, $P< 0.05$), and MUSTN1 (24 h, 4.3-fold, $P < 0.05$).
<>We examined whether FBXO32/atrogin-1/MAFbx, a known regulator of protein breakdown and of muscle atrophy was differentially expressed: the gene was downregulated after lengthening contractions (3 h, 2.7-fold, $P < 0.05$; 6 h, 3.3-fold, $P< 0.05$; 24 h, 2.3-fold, $P < 0.05$). The results suggested that lengthening and shortening contractions activated distinct molecular pathways as early as 3 h postexercise. The molecular differences might contribute to mechanisms underlying the physiological adaptations seen with training using the two modes of exercise."[489]

[B] Superslow resistance training enhances muscle strength more than regular-speed resistance training.

"<>Background: The study assessed a way to increase the intensity and effectiveness of resistance training by comparing training with a slower repetition speed to training with a conventional repetition speed. Slower repetition speed may effectively increase intensity throughout the lifting phase while decreasing momentum. Methods: Two studies were done with untrained men (N=65) and women (N=82), (mean age=53.6) who trained two to three times per week for eight to 10 weeks on a 13 exercise Nautilus circuit performing one set of each exercise. Participants exclusively trained using regular speed repetitions for 8 to 12 repetitions per set at 7 sec each (2 sec lifting, 1 sec pause, 4 sec lowering) or a Super Slow training protocol where they completed 4 to 6 repetitions per set at 14 sec each (10 sec lifting, 4 sec lowering). All of the participants were tested for either the 10 repetition-maximum (RM) weightload (regular-speed group) or the 5-RM weightload (slow-speed group).
<>Results: In both studies, Super-Slow training resulted in about a 50% greater increase ($p<0.001$) in strength for both men and women than regular speed training. In Study 1, the Super-Slow training group showed a mean increase of 12.0 kg and the regular speed group showed an increase of 8.0 kg increase ($p<0.001$). In Study 2, the Super-Slow training group showed a 10.9 kg increase, and the regular speed group showed an increase of 7.1 kg ($p<0.001$).
<>Conclusions: Super-Slow training is an effective method for middle-aged and older adults to increase strength. Although studies still need to be done with at-risk populations, repetition speed should be considered when prescribing resistance training."[490]

[C] Eccentric + Superslow Concentric resistance training promotes greater MRF release than regular-speed resistance training, whether this is due to increased muscle damage or another mechanical response to training I do not know.

"<>We aimed to determine if the time that muscle is under loaded tension during low intensity resistance exercise affects the synthesis of specific muscle protein fractions or phosphorylation of anabolic signalling proteins. Eight men (24 ± 1 years (sem), BMI = 26.5 ± 1.0 kg m−2) performed three sets of unilateral knee extension exercise at 30% of one-repetition maximum strength involving concentric and eccentric actions that were 6 s in duration to failure (SLOW) or a work-matched bout that consisted of concentric and eccentric actions that were 1 s in duration (CTL). >Participants ingested 20 g of whey protein immediately after exercise and again at 24 h recovery. Needle biopsies (vastus lateralis) were obtained while fasted at rest and after 6, 24 and 30 h post-exercise in the fed-state following a primed, constant infusion of l-[ring-13C6]phenylalanine. Myofibrillar protein synthetic rate was higher in the SLOW condition versus CTL after 24–30 h recovery ($P < 0.001$) and correlated to p70S6K phosphorylation ($r = 0.42$, $P = 0.02$). Exercise-induced rates of mitochondrial and sarcoplasmic protein synthesis were elevated by 114% and 77%, respectively, above rest at 0–6 h post-exercise only in the SLOW condition (both $P < 0.05$). Mitochondrial protein synthesis rates were elevated above rest during 24–30 h recovery in the SLOW (175%) and CTL (126%) conditions (both $P < 0.05$).
<>Lastly, muscle PGC-1α expression was increased at 6 h post-exercise compared to rest with no difference between conditions (main effect for time, $P < 0.001$). These data show that greater muscle time-under-tension increased the acute amplitude of mitochondrial and sarcoplasmic protein synthesis and also resulted in a robust, but delayed stimulation of myofibrillar protein synthesis 24–30 h after resistance exercise."[491]

Detraining, Deloading, & Vascular Deconditioning

Why is it that power athletes today are on protocols with more rest days (144h+) in-between workouts, and experience greater benefits, especially towards muscle force production? Is this not proof they are facilitating complete myogenesis? I would have to argue that in line with the research, detraining promotes myogenesis through enhancing protein synthesis by resetting myogenic muscle genes, through promoting fast twitch muscle fiber transcription factors, and more rest days allow you to form new myotubes, and new "anchors" to your myofibrils, costameres. There is the benefit for less frequent workouts for explosive athletes [See: Muscle Fiber Types], and there is also the benefit of resetting angiogenic genes or processes within the muscles during detraining, so that exercise-induced angiogenesis does not plateau.

Deloading is often added to a workout protocol too late for it to benefit an individual, and more often than not deloading is considered by most Guru's to be lifting 60-70-80% your 1RM, which is an extremely foolish idea. Deloading should be performed at near-Lactic acid Training percentages or below.

Tom Platz would only squat once a week, and although he no doubt overtrained his leg muscles, they had ample time to recover between workouts do to his steroid use. On a related note, regarding Platz, a puzzling concern, why did his legs grow more than his biceps or other muscles? I would hypothesize that because he trained his arms multiple times per week, giving them insufficient time to recover, they did not experience the same benefits his leg muscles did. If you Deload or Detrain and still do not achieve results in the gym, you are clearly causing too much damage to your muscle tissue and should stick with Lactic Acid Training for a year or more.

To reset exercise-induced angiogenesis, which I will remind you only occurs during high volume exercise such as Aerobics, Cardio, B.F.R. training, LAT, I suggest you detrain for seven days, including eliminating all Pro-Inflammation modalities, and supplementation, every few months. But only do this after spending time growing and hypertrophying your muscle capillaries through frequent angiogenic training, to avoid severe Vascular Deconditioning.

[A] Exercise-induced angiogenesis begins to decline at around 4-Weeks of very high-frequency (three days a week, to four days, to five days), high intensity cardio training exercise. Although this doesn't take into account B.F.R. Training or modalities, it is still extremely important information for those on the Pro-Cycle that detraining for three to four days per 4-weeks, or at the very, deloading with very light aerobics i.e. warmups only, is suggested to maintain exercise-induced capillarization (angiogenesis).

"<>In summary, this study demonstrates that intense intermittent endurance training induces an increase in endothelial cell proliferation and an increased capillarization that is equally distributed around type I and type II fibres in human skeletal muscle. The capillary growth occurs within 4 weeks and appears to be transient, as evidenced by a reduction in proliferating endothelial cells and no further capillarization after 7 weeks of training. Proliferative compounds other than VEGF are released in response to exercise and are likely to be important for training-induced angiogenesis. VEGF and bFGF were localized in skeletal muscle cells, with VEGF also present in the majority of capillaries, but the distribution of these growth factors was not found to be altered during the training period."[491.1]

[B] Detraining restores intramuscular anabolic signaling.

"<>Resistance training-induced muscle anabolism and subsequent hypertrophy occur most rapidly during the early phase of training and become progressively slower over

time. Currently, little is known about the intracellular signaling mechanisms underlying changes in the sensitivity of muscles to training stimuli. We investigated the changes in the exercise-induced phosphorylation of hypertrophic signaling proteins during chronic resistance training and subsequent detraining. Male rats were divided into four groups: 1 bout (1B), 12 bouts (12B), 18 bouts (18B), and detraining (DT). In the DT group, rats were subjected to 12 exercise sessions, detrained for 12 days, and then were subjected to 1 exercise session before being killed.
<>Isometric training consisted of maximum isometric contraction, which was produced by percutaneous electrical stimulation of the gastrocnemius muscle every other day. Muscles were removed 24 h after the final exercise session. Levels of total and phosphorylated p70S6K, 4E-BP1, rpS6, and p90RSK levels were measured, and phosphorylation of p70S6K, rpS6, and p90RSK was elevated in the 1B group compared with control muscle (CON) after acute resistance exercise, whereas repeated bouts of exercise suppressed those phosphorylation in both 12B and 18B groups. Interestingly, these phosphorylation levels were restored after 12 days of detraining in the DT group.
<>On the contrary, phosphorylation of 4E-BP1 was not altered with chronic training and detraining, indicating that, with chronic resistance training, anabolic signaling becomes less sensitive to resistance exercise stimuli but is restored after a short detraining period."[492]

[C] Resistance Training a muscle within its 72h recovery period results in decreased anabolic signaling through eIF4E/eIF4G, downstream proteins of mTOR & ERK.

"Insufficient duration of recovery between resistance exercise bouts reduces the effects of exercise training, but the influence on muscle anabolic responses is not fully understood. Here, we investigated the changes in the distribution of eukaryotic initiation factor (eIF) 4E, a key regulator of translation initiation, and related factors in mouse skeletal muscle after three successive bouts of resistance exercise with three durations of recovery periods (72 h: conventional, 24 h: shorter, and 8 h: excessively shorter). Bouts of resistance exercise dissociated eIF4E from eIF4E binding protein 1, with the magnitude increasing with shorter recovery. Whereas bouts of resistance exercise with 72 h recovery increased the association of eIF4E and eIF4G, those with shorter recovery did not. Similar results were observed in muscle protein synthesis. These results suggest that insufficient recovery inhibited the association of eIF4E and eIF4G, which might cause attenuation of protein synthesis activation after bouts of resistance exercise."[493]

[D] Unilateral Training prevents atrophy of the opposite limb, an important piece of information for those who are injured and disinterred in training for fears of asymmetry developing.

"<>Cross education (CE) occurs after unilateral training whereby performance of the untrained contralateral limb is enhanced. A few studies have shown that CE can preserve or "spare" strength and size of an opposite immobilized limb, but the specificity (i.e.,

trained homologous muscle and contraction type) of these effects is unknown. The purpose was to investigate specificity of CE "sparing" effects with immobilization. The nondominant forearm of 16 participants was immobilized with a cast, and participants were randomly assigned to a resistance training (eccentric wrist flexion, 3 times/week) or control group for 4 weeks. Pre- and posttesting involved wrist flexors and extensors eccentric, concentric and isometric maximal voluntary contractions (via dynamometer), muscle thickness (via ultrasound), and forearm muscle cross-sectional area (MCSA; via peripheral quantitative computed tomography).
<>Only the training group showed strength preservation across all contractions in the wrist flexors of the immobilized limb (training: -2.4% vs. control: -21.6%; P = 0.04), and increased wrist flexors strength of the nonimmobilized limb (training: 30.8% vs. control: -7.4%; P = 0.04). Immobilized arm MCSA was preserved for the training group only (training: 1.3% vs. control: -2.3%; P = 0.01). Muscle thickness differed between groups for the immobilized (training: 2.8% vs. control: -3.2%; P = 0.01) and nonimmobilized wrist flexors (training: 7.1% vs. control: -3.7%; P = 0.02). Strength preservation was nonspecific to contraction type (P = 0.69, [Formula: see text] = 0.03) yet specific to the trained flexors muscle. These findings suggest that eccentric training of the nonimmobilized limb can preserve size of the immobilized contralateral homologous muscle and strength across multiple contraction types.
<>NEW & NOTEWORTHY Unilateral strength training preserves strength, muscle thickness, and muscle cross-sectional area in an opposite immobilized limb. The preservation of size and strength was confined to the trained homologous muscle group. However, strength was preserved across multiple contraction types."[493.1]

Vascular Deconditioning (Capillary Regression)

The blood vessels that are formed through high frequency training are often lost during extended detraining, making it necessary to train every muscle twice a week at the very least on a Pro-Cycle to maintain muscle capillarization.

It is important to mention that you do not need to engage in HIT or intense training to maintain muscle capillarity as even performing warmups with very low loads and high repetitions will be enough to protect your blood vessels from regression during periods of inactivity, especially if you learn to accumulate lactic acid during your resistance training. If training is never avoided and a sufficient number of different exercises are performed every workout with enough volume, it should be possible to carryover and maintain the accrued muscle capillaries that are formed during a Pro-Cycle to an Anti-Cycle, and then back again, although it is my opinion that capillaries that are formed and grown through consistent angiogenic training over the course of many months will be more resistant to regression during periods of detraining, similarly to muscle tissue, but to be safe each muscle should be trained twice per week to maintain capillary density.

[A] One week of detraining is enough time to cause muscle capillary regression to pre-training levels.

"<>The purposes of this study were as follows: (1) to examine basal vascular endothelial growth factor (VEGF) protein concentrations following 10 weeks of endurance training and after 7 days of detraining; and (2) to examine the acute VEGF protein response to a single 1 h exercise work bout in trained and detrained animals in relationship to changes in capillary indices following training and detraining. Thirty-three Sprague-Dawley rats were randomized into the following six groups: (1) control-basal; (2) control-acute exercise; (3) trained-basal; (4) trained-acute exercise; (5) detrained-basal; and (6) detrained-acute exercise.
<>Groups 3-6 performed endurance training on a rodent treadmill three times per week for 10 weeks. Following the training intervention, rats in groups 5 and 6 remained cage confined (i.e. detrained) for 7 days. As expected, training increased soleus and plantaris muscle capillarity and attenuated the VEGF response to acute exercise. Seven days of detraining, however, resulted in a regression of capillary contacts and individual capillary-to-fibre ratio in the plantaris and soleus muscles compared with the trained group ($P < 0.05$). Restoration of the VEGF protein response to acute exercise was evident in both muscles, but only statistically significant in the plantaris muscle ($P < 0.05$).
<>This is the first study to demonstrate the temporal relationship between VEGF protein expression and skeletal muscle capillarity within the first week of detraining. The findings of the present investigation are consistent with the hypothesis that reduced capillarity impairs oxygen availability to the working muscles. The results indicated that training-induced angiogenic remodelling was reversible following 1 week of detraining and may be modulated by VEGF."[493.2]

[B] A loss in muscle capillarity interestingly results in insulin resistance, making it necessary to restrict carbohydrate consumption during detraining.

"<>Muscle insulin resistance is associated with a reduction in vascular endothelial growth factor (VEGF) action and muscle capillary density. We tested the hypothesis that muscle capillary rarefaction critically contributes to the etiology of muscle insulin resistance in chow-fed mice with skeletal and cardiac muscle VEGF deletion (mVEGF(-/-)) and wild-type littermates (mVEGF(+/+)) on a C57BL/6 background. <>The mVEGF(-/-) mice had an ~60% and ~50% decrease in capillaries in skeletal and cardiac muscle, respectively. The mVEGF(-/-) mice had augmented fasting glucose turnover. Insulin-stimulated whole-body glucose disappearance was blunted in mVEGF(-/-) mice. The reduced peripheral glucose utilization during insulin stimulation was due to diminished in vivo cardiac and skeletal muscle insulin action and signaling. The decreased insulin-stimulated muscle glucose uptake was independent of defects in insulin action at the myocyte, suggesting that the impairment in insulin-stimulated muscle

glucose uptake was due to poor muscle perfusion. The deletion of VEGF in cardiac muscle did not affect cardiac output. <>These studies emphasize the importance for novel therapeutic approaches that target the vasculature in the treatment of insulin-resistant muscle."[493.3]

IMC Recovery Periods

The recovery periods on the following page are the days I suggest should be spaced between specific loads lifted, such that Max, Near-Max, Very-High, High, & Moderate-High Loads will never be lifted twice in a week (unless you engage in partial ROM training). Detraining times increase alongside 1RM increases, such that you will not train a muscle at all to facilitate maximal recovery, although warmup percentages (VLL) can be lifted during the detraining periods to facilitate slow twitch muscle regeneration, you will still need to detrain properly at some point as muscle damage does accumulate over time regardless of loads lifted.

If you wish to develop your muscles with the greatest efficiency through higher load training, you should always alternate between higher loads and lower loads every workout, unless you are following a classical periodization protocol, such as my 15P Protocol. Even considering Wave Training, it is still important to program periods each year where you deload properly, *not with high loads*, but with very low loads (30, 15, 5%), to allow your muscles time to recover to the greatest and safest degree. There is no doubt that to accrue and maintain absolute strength will require far more dangerous and classically programmed deloading, such that you may never lift below 60% your 1RM, and if power is your only goal you should obviously hire a powerlifting coach, but do not be surprised when you experience a serious injury as the body was not designed to lift high loads for extended periods of time.

On a Pro-Cycle, these recovery periods and their detraining times may be partially disregarded, primarily for the detraining recommendations for Moderate Loads or anything lighter, such that you should go for a light swim, a hike, walk on a treadmill, bicycle around town, do some moderate-intensity boxing, or specialized / full body warmups multiple times per week, or ideally, every day, to promote Aerobic exercise-induced muscle angiogenesis and accelerate slow twitch fiber and *potentially* fast twitch fiber regeneration. You must remember, Aerobic exercise although being time consuming, and if performed with traditional resistance exercises, which owing to the super light weights lifted will be possibly embarrassing for some, will offer you the greatest increase to health resilience, and muscle function throughout lifespan, most importantly if you are a natural athlete. As I always suggest to people I know, and have to remind myself, it is far better to skip a higher load or higher intensity workout as long as Thorough Warmups were performed earlier in the day, as these "Warmup" workouts, are still to be considered a *sufficient workout*, even if many of these sessions will be

categorizable as undertraining, we must never consider lifting light weight as "Suboptimal" as some foolish people have labeled them because low load training is the *most* optimal form of training in existence.

Regular-speed Resistance Training

- Max Loads (ML): 90-105% 1RM: 192h (8-Days) Recovery. 96h Detraining.
- Near-Max Loads (NML) 75-90% 1RM: 168h (7-Days) Recovery. 96h Detraining.
- Very-High Loads (VHL) 60-75% 1RM: 144h (6-Days) Recovery. 96h Detraining.
- High Loads (HL) 45-60% 1RM: 120h (5-Days) Recovery. 72h Detraining.
- Moderate-High Loads (MHL) 30-45% 1RM: 96h (4-Days) Recovery. 72h Detraining.
- Moderate Loads (ML) 15-30% 1RM: 72h (3-Days) Recovery. 72h Detraining.
- Light Loads (LL) 5-15% 1RM: 48h (2-Days) Recovery. 48h Detraining.
- Very Light Loads (VLL) 1-5% 1RM: 0h (0-Day) Recovery. No Detraining (48-72h Every other week).

Extreme Tempo Superslow Training Resistance Training

- Max Loads (ML): 90-105% 1RM: 336h (14-Days) Recovery. 120h Detraining.
- Near-Max Loads (NML) 75-90% 1RM: 288h (12-Days) Recovery. 120h Detraining.
- Very-High Loads (VHL) 60-75% 1RM: 240h (10-Days) Recovery. 120h Detraining.
- High Loads (HL) 45-60% 1RM: 192h (8-Days) Recovery. 96h Detraining.
- Moderate-High Loads (MHL) 30-45% 1RM: 144h (6-Days) Recovery. 96h Detraining.
- Moderate Loads (ML) 15-30% 1RM: 96h (4-Days) Recovery. 96h Detraining.
- Light Loads (LL) 5-15% 1RM: 72h (3-Days) Recovery. 72h Detraining.
- Very Light Loads (VLL) 1-5% 1RM: 48h (2-Day) Recovery. 48h Detraining.

Important: The Recommended Intervals between workouts are dependent on loads lifted and are for optimal recovery between workouts i.e. muscle growth, tendon growth, and the protection of the joints. These Recovery and Detraining Periods are not designed for maximizing Central Nervous System or Myoneural Junction adaptation, which will require higher frequency training. The time periods below are to be paired with workouts composed of the specified percentages and an assumed moderate-high training volume for each workout (multiple sets).

Recovery Periods are not the same as Detraining Periods, Recovery Periods equate to the suggested time between lifting similar percentages (deloading), whereas Detraining Periods equate to the recommended minimum healing time a muscle requires between workouts where you do not train it at all. Occasionally these time periods will align, which may confuse some individuals.

Progressively Dispersed Detraining

When detraining becomes too complex a variable to incorporate into your workout protocols, an idea I have produced is to begin a workout protocol at low loads and a high frequency of training, progressively decreasing the exercise frequency while increasing the loads lifted, thus every fourth, fifth, sixth, or seventh week you will only be training a muscle once with high loads thereby allowing ample detraining time. This can be visualized in my Inverse Correlation Exercise protocol in the Workout Protocols section.

Overtraining

It is my hypothesis that the less secondary myotubes you have, the more force you are able to produce due to having less overall muscle tissue, explained by:

1. Maximized neuromuscular synapse activity due to increased Hennemans Size Principle, which states smaller muscle fibers are recruited first, followed by larger. This being due to having less secondary myotubes from overtraining, resulting in hypertrophied primary myotubes that possess an amplified ability to generate force.
2. Higher density of sarcomeres, leading to greater force transmission[1].
3. Greater myofibril connectivity through enhanced costamerogenesis (myofibril anchors).
4. Due to specialized “overtraining”, athletes that participate in explosive or endurance sports will have greater control over muscle fiber type, by promoting only the growth of fast or slow twitch fibers, leading to preferential myogenic growth.

The primary ways to destroy secondary myotubes is through overtraining and alcohol consumption (fast twitch fiber atrophy). Purposeful Overtraining is not a new concept as the *Bulgarian Method* has been around for over thirty years (training muscles intensely twice or more per day), but we must understand it is only effective in athletes who are on anabolic steroids and use explosive training, as explosive (concentric) muscle contractions are the least damaging, not only because of the reduced time-under-tension that accompanies an explosive exercise, but because of the reduction in muscle fiber recruitment, as the momentum generated during the earliest contraction (the strain on a relatively small part of a muscle), leads to less strain during the range of motion on the resulting muscles that must contract, leading to greater damage occurring in the

beginning of an exercises ROM, and less overall damage to the entirety of muscle, invariably resulting in less myogenic stem cells being necessary to regenerate the damaged muscles. But even non-explosive Regular-speed resistance *overtraining* is liable to enhance muscle force generation, at the higher risk of injury due to greater muscle damage.

The safest form of overtraining is to use the ascending (proximal) parts of a muscle i.e. Partial Range of Motion movements such as Board Presses or Box Squats, thus protecting the tendons and joints, and most sensitive parts of your muscles.

Overtraining for the purposes of enhancing muscle function & hypertrophy by destroying more muscle tissue than can be recovered can be explained in this analogy I devised:

Each muscle fiber is a skyscraper, contraction of a muscle fiber results in muscle fiber damage, contraction (exercise) is to be considered a "storm" that results in skyscraper exterior damage. When a skyscraper is damaged a limited number of construction crew members (stem cells) enter into the damaged building and begin rebuilding it, if the crew is too small, the building will either not be repaired efficiently and remain permanently damaged or be returned to a near-original state of function (growth plateau). If the crew is large enough, the building will not only be repaired, but reinforced (hypertrophied) with extra layers of steel (secondary myotubes) being applied to the structure. The amount of available construction crew members is manipulatable through many external factors such as *increased pay* (chemical facilitators). The cities with fewer skyscrapers (primary myotubes) & skyscrapers with lessened reinforcement (secondary myotubes) due to experiencing chronic and frequent storms will have better *communications* (neuromuscular junction function) than the cities with more skyscrapers, because these reinforcements interfere with the strength and reach of communications between skyscrapers.

Now think of a city with numerous skyscrapers of variegated sizes, and different levels of reinforcements, this is muscle tissue. The greater number of storms (exercise sessions) that occur in your city (body), and the greater the force (resistance) of the storms that occur in your city, the more skyscrapers will be damaged.

Although the cities which experience subchronic storms (optimal exercise training) will have impressively reinforced skyscrapers (hypertrophy), they do not have strong communication to the other skyscrapers. And for the cities which experience chronic storms (overtraining), the density of reinforcements will be lesser, but they will have increased communication to the other skyscrapers, at the cost of substantially increased risk of developing or harboring progressively worsening dysfunctional infrastructures (primary myotube damage) due to the damaged building foundations (fibrosis, senescence, damaged mitochondria, atrophy, or apoptosis).

A life without overtraining would equate to less absolute power, endurance, and explosivity, because in a way it is indicative of the process of Synaptic Pruning that occurs during early childhood, whereby synapses are eliminated to make way for personality and behaviors to form (Exercise is, in a way, a type of *behavior*, one that varies in intensity). Myostatin therefore is to be considered a *Myogenic Pruning Agent*, used by the body to prevent the unnecessary growth of lean muscle tissue, which if inhibited from birth to adulthood would render us not only inflexible (supranormal muscle mass / tendon brittleness), but potentially immobile, and easy prey. Conversely, overtraining when utilized too frequently, as is the case with most gymgoers, will result in plateaus and fitness regression, and later life musculoskeletal dysfunction.

I'd like to mention that I often notice recreational gymgoers use high intensity-high load resistance training as a neurotrophic replacement for cardiovascular exercise. There is clearly a large difference in muscle damage and sustainability of exercise choice between *squatting* versus *cycling* at high resistances and high intensities, it is therefore quite foolish to engage in high intensity strength training for extended periods of time to improve mood and memory, whereas it would be far more intelligent to keep strength separate from cardio—to separate exercise by body and mind. mTOR and AMPK, although working in concert during myogenesis, are best upregulated separately through specific training protocols. Utilizing high intensity strength training as a way to promote high heart rate-induced neurogenesis and post-exercise boosts to mood, memory, and confidence creates a dangerous habit that will predispose you to injury.

[1] "<>One of the most fundamental properties of skeletal muscle is that the amount of force it generates depends on its length. This work was elucidated at the single fiber level in the classic studies by Gordon et al. In this relationship, skeletal muscle fiber force production is defined in terms of myofilament overlap, i.e. in terms of sarcomere length. At optimal length, where actin–myosin interactions are maximal, muscle generates maximum force. As sarcomere length increases, force decreases owing to the decreasing number of interactions between actin and myosin myofilaments. At lengths shorter than the optimum, force decreases owing to double interdigitation of actin filaments with both myosin and actin filaments from opposite sides of the sarcomere. While this relationship has been challenged, to a first approximation, muscle force generation can be considered as a direct function of sarcomere length, and whole muscle force generation results from the aggregate force produced by all of the sarcomeres. Exceptions to this rule are likely to be small in magnitude and method-dependent."[494]

The study below describes the two different types of satellite cell expansions during healthy muscle repair: Asymmetric or Symmetric. The former process occurs in minimally damaged muscle, and the latter process occurs in severely damaged muscle. The more frequently you severely damage your muscles through overtraining, the faster you will lose "stemness", this being due to an inability for your stem cells to re-enter a

quiescent state. There is no doubt that there is extreme nuance here, in that a person that consistently exercises, even if too much, will be healthier and stronger in old age than their polar opposite, but injuries aside, the person who consistently plans their workouts carefully, intelligently, by saving their hardest training sessions for far briefer training periods, and incorporates a sufficient amount of detraining periods to allow optimal stem cell quiescence, will undoubtedly have healthier stem cell populations in old age. Recreational athletes are often misguided by steroid users who train in very specific ways, at very high intensities and frequencies, those who have unnaturally high levels of stem cells available to overtrain consistently, which allows them the physiological leeway to hypertrophy from terribly planned workout protocols. For myogenic longevity, as a natural lifter, you must learn to either use reduced ROM's (geared lifting), or use lower loads for the majority of your workouts as you age, you are at a severe disadvantage, and blindly following the guidance of your *hypertrophied idols* will only bring you dissatisfaction.

"<>In response to injury or inflammation, satellite cells will activate and enter the cell cycle to begin dividing and creating new cells for regeneration. Depending on the degree of regeneration required, satellite stem cells (Pax7+/Myf5−) will change their preference for asymmetric self-renewal or symmetric expansion of the stem cell pool. Under normal homeostatic turnover or minor damage, satellite cells preferentially undergo asymmetric division that will produce one stem cell (Pax7+/Myf5−) and one committed cell (Pax7+/Myf5+), which can then become a progenitor and undergo successive rounds of division.

<>Conversely, under more severe circumstances where damage is greater and demand for regenerative cells higher, satellite stem cells initially undergo symmetric division in order to rapidly expand the stem cell pool to facilitate large-scale generation of progenitors through asymmetric division.

<>Under homeostatic conditions or following injury when active muscle repair is no longer required, satellite cells must be able to exit the cell cycle and enter a reversible state of quiescence to preserve and maintain long-term regeneration potential of its resident muscle. Multiple studies have demonstrated that the loss of quiescence and the ability to exit and re-enter quiescence leads to a loss of 'stemness', homeostatic decline of the satellite cell population, and eventual inability to regenerate damaged muscle."[494.1]

Load Volume Tracking / Training (LVT/T)

LVT/T is an intriguing way to keep track of your body's adaptation to training based on the *Load Volume* (LV) of the workout, it is simply the act of journaling the total pounds lifted in a workout, especially of the working sets.

There is no doubt that this sort of exercise tracking and training methodology is useless if you incorporate different exercises and different tempos into a workout as the added

variables will make LVT/T far too inaccurate to be considered even a slightly viable training adaptation measurement system. If you intend on using LVT/T, remember to stick with the same exercise, the same tempo, and steady weight within a workout for an extended period of time (multiple weeks), to collect more accurate data. Even with fewer variables LVT/T will never be entirely accurate or beneficial to all individuals, but it is still an interesting way to experiment with resistance training volume.

I will suggest also that the loads lifted during warmups not be tracked and combined with the higher loads lifted during classical strength training, unless you are only lifting very low loads in a workout. If you follow my previous guidance regarding optimal exercise warmups then the total pounds of weight you will be lifting during these warmups will be meager and inconsequential compared to the pounds of weight you will lift during your working sets of resistance exercise. Warmup exercises, if low enough in load, should never be restricted due to constraints in LV.

Ideally you would combine LVT/T with an exercise protocol that involves one compound or one isolation movement, one tempo type, one ROM type, and steady weight training i.e. Sets of 3-Reps, 5-Reps, 6-Reps: Never Overload training (workouts where you attempt to test or surpass your 1RM).

Say for example your goal is to increase your bench press 1RM which is currently 400lbs, and you followed the periodization workout protocol below which lead up to a failed new 1RM attempt and a 400lb plateau:

Week 1: (2250LB LV)
Mon: Bench Press: 250LB - 3-Sets x 3-Reps.
Fri: Bench Press: Occlusion Training.

Week 2: (2700LB LV)
Mon: Bench Press: 300LB - 3-Sets x 3-Reps.
Fri: Bench Press: Occlusion Training.

Week 3: (3150LB LV)
Mon: Bench Press: 350LB - 3-Sets x 3-Reps.
Fri: Bench Press: Occlusion Training.

Week 4: (????LB LV)
Mon: Bench Press: NEW 1RM FAIL.
Fri: Bench Press: Occlusion Training.

In Week 4 you attempted but failed to break your bench press 1RM, but you kept track of your previous weeks' Load Volume, and because of that you would be able to easily experiment with changes to your workout Load Volume. Assuming that your plateau in

1RM growth is not due to technical or CNS insufficiency, you can begin experimenting with changes to your Load Volume by firstly assuming you are overtraining and decrease each workouts total LV, such that you will set a lower LV limit than previously for each workout, except for the final overload workout, maybe that is 2000LB's, 1800LB's, or even 1500LB's. If dropping the Load Volume of the majority of your workouts increases your absolute strength or even your multi-repetition / multi-set strength (3RM, 5RM, 6RM, etc.) then you have found the optimal anabolic stimulus of volume to facilitate adaptation through training.

You can use LVT/T in two different creative ways, the first is to set a LV Limit to not exceed in a workout and train by how you feel (such as by setting a limit of 1500LB Total Load Volume for the Bench Press), the second way to use LVT/T is to attempt to maintain and match an *exact* LV each workout, which will offer the greatest accuracy in measuring your adaptation or maladaptation to your training.

Infrequently you may wish to increase the Load Volume of a workout to overtrain purposefully, and it is my opinion that the best and safest way to do this is to increase the Load Volume of an average workout by 25% for a period of three-four weeks, or to increase the LV of an average workout by 50% for a period of one-two weeks. This is only suggested to be done immediately after a plateau is reached, to tax and train the CNS.

The Glycogen Rubicon Principle

The glycogen within muscles serve as an *anabolic meter* for high intensity exercise, for when our muscle and possibly liver glycogen stores are exhausted, the processes of proteolysis and lipolysis are stimulated. Proteolysis is preferentially activated during low intensity exercise with low glucose availability e.g. when glycogen stores and blood glucose are low, where the demand for energy is not met through the *slow metabolic breakdown* of fat, but muscle breakdown also occurs through high load or high intensity training, wherein the muscle damage can exceed the myogenic potential of a human beings biological system, and this is primarily explained by insufficient stem cell pools and stem cell recruitment. High volume-low intensity exercise burns more fat over time through promoting long-lasting cellular adaptations. Lipolysis is preferentially activated during high intensity exercise, where the demand for energy exceeds the bodies steady supply, but energetic adaptation is transient, and precisely like proteolysis, complicated by the variable of overtraining.

To summarize the previous points, glycogen exhaustion signals to our body we are in an energy crisis, and so both proteolysis and lipolysis are stimulated to much greater degrees of activity than homeostasis would prefer. When the best athletes in world suggest training for shorter periods of time results in greater anabolic potential, they are unconsciously expressing what I refer to as the *Glycogen Rubicon Principle*, which

explains the switch from anabolism to catabolism that accompanies low volume versus high volume exercise.

It is true that training with low glycogen stores, and low blood glucose will enhance IL-6 release, but IL-6 primarily acts upon slow twitch muscle fibers to promote growth, whereas fast twitch fibers require a constant influx of glucose to maintain their purest phenotype. This of course does not mean IL-6 is only anabolic in slow twitch fibers, it clearly enhances the anabolic milieu required for optimal muscle regeneration.

For maximal stimulation of fast twitch fiber anabolism, glycogen stores must never be completely exhausted during exercise, or at the very least once exhausted, the muscles must be immediately refueled with carbohydrates. Regarding diet, bodybuilders have it down to a precise science, but it is not very complex, one must simply consume carbohydrates each meal, and ideally consume a liquid carbohydrate drink intra-workout. The more liquid carbohydrates consumed in a workout, the greater the rest periods between sets, the less glycogen exhaustion will occur, and the greater the expression of mTOR will be post-exercise.

To engage in Lactic Acid Training, which promotes fast twitch fiber growth, during a carbohydrate-rich diet will require that your exercise intensity increase (load or volume) due to the magnified threshold of Aerobic metabolism facilitated through increased metabolic energy availability.

Following this principle for extended periods of time is no doubt unhealthy, but beneficial for the maximization of fast twitch fiber growth.

IMC Exercise Warmups

If it isn't clear to you, warming up before an intense exercise session is essential for optimized muscle growth and injury prevention. The majority of Exercise Warmups should be performed with a Normal-Slower Tempo (Not Explosive), and without long rest periods, to accumulate lactate & blood in your muscles, and prepare the muscle tissue for a ***more intense molecular response*** [1].

What a warmup should entail in my opinion is using 5% or less of your 1RM (no higher!) for 5-10 Sets of 30-80 Reps per exercise, never dropping below 500 Repetitions total per muscle group spread out across numerous exercises and many, many sets, such that if you're warming up your biceps, you could do 3-Sets of 40 Repetitions of pronated biceps curls, then 3-Sets of 50 Repetitions of supinated biceps curls, X # of sets of drag curls, X # of sets of partial biceps curls, X # of sets of Zottman curls, et cetera. It's important to not focus on a certain rep range each set, ideally you will accumulate enough lactate in the muscles that will signal your set is over, or you will feel an adequate "pump", which is simply active hyperemia (enhanced muscular blood flow). It must be clarified that 1RM percentages do not and should not necessarily apply to warmups, especially when dozens of different exercises are performed, as not many people max out on every different exercise variation, but I can suggest confidently, with experience, that

for the average gymgoer, for upper body warmups, especially for safe aerobic resistance warmups, there is no need to surpass a weight of 2LB's for dumbbells if you wish to avoid unintended overtraining, or if you are physically weak, minimally muscular, or a woman, and 4LB for dumbbells if you are extremely strong, powerful, and / or muscular. If you use machines or cables to warmup your muscles you will have to lift heavier weights considering most machines start at 10LB's or resistance or higher, which is fine for those with developed bodies, but insufficient for those with injuries, weaknesses, or *stem cell impoverishment* (females, low testosterone males, the elderly, or people who prefer training safely with super low loads).

Often times you will not be able to accumulate lactic acid in a muscle group even when training with very low loads, and this may be because you are overtrained, the exercise or exercise form you are utilizing is inefficient or does not allow optimal time-under-tension, your tempo is too slow or too fast, or you are mentally exhausted and lack the mind-muscle connection to maintain adequate time-under-tension, and on these days you can simply pursue the hyperemia *pump* that accompanies high volume low load training.

You'll know when you have performed enough warmup exercises for a muscle group when you begin to feel relatively weak after a few hundred repetitions, as this is a sign that you have begun to tap into and exhaust your muscle glycogen stores.

Lifting with a much faster tempo may promote greater lactic acid accumulation at times, but generally these type of explosive movements are not effective warmups, considering explosive lifting only targets a small amount of muscle tissue, whereas the rest of the muscle that is intended to be trained is carried by momentum, thus leading to the development of "sticking points", or injuries.

An important benefit of having a long & complex warmup period i.e. one involving using a multitude of exercises, is that you're training all the muscle fibers within a muscle group in a gentle way, thus preventing muscle atrophy, which is important if you are one who specializes in a certain exercise or subset of exercises, such that a cyclist will be able to maintain upper body hypertrophy while focusing his energies (stem cells / neurotransmitters) on his leg training, selfsame to a bench press specialist who will be able to maintain lower body hypertrophy during an intense protocol. Unfortunately, many people who exercise are still under the impression that *one exercise* is capable of working an entire individual muscle, such that a person who squats will suggest that they have fully exhausted their leg muscles, when in fact they have only stimulated the middle part of their hamstrings and upper part of their quadriceps (rectus femoris), and maybe a little bit of the adductors. Do remember there is not one single exercise that will activate all parts of a muscle, for example: Biceps curls activate either the lower (distal) or higher (proximal) biceps muscles depending on the elbow angle (retraction or protraction), Biceps curls also activate either the short head or long head depending on wrist rotation, therefore you should always have a *minimum* of two isolation exercises per muscle, ideally three or four, in combination with numerous compound exercises.

To maximize lactic acid production, consider using Quarter Reps, Middle Reps, & Partial Reps in your compound and isolation exercises to maintain tension in the muscles. These reduced ROM exercises are especially important when lifting very light weights, as the only other option to increase time-under-tension with low loads is Superslow Training, but this defeats the angiogenic benefit of Lactic Acid / Aerobic Training. Furthermore, Isolation exercises are the best exercises to warmup with, because as you will be using very low loads, maintaining tension will be easier, especially with free weights, and the mind-muscle connection is inherently stronger when we train less muscles at one time.

I wish to reinstate that warmups should be performed at the lightest weight possible necessary to accumulate blood and lactic acid within muscle tissue, that means performing sets of six, twelve, or twenty repetitions with heavy weight are not to be considered useless warmups but are nonetheless counterintuitive, as they are not ideal Exercise Warmups, as most warmup sets should be between *thirty to eighty repetitions* with set failure coming from lactic acid pain, subjective muscle hyperemia, or neurotransmitter exhaustion. If you feel embarrassed about lifting light weights in public remember there is no room for insecurity on the path to greatness.

If you are a personal trainer, and your client is elderly or very young, and you are training them with "high loads" i.e. a weight that they can only manage three to twelve repetitions with, when proper formed has not yet been mastered, and antagonist muscles have not been developed, you are a fool. Weak bodies must always first be tempered through endless repetition (volume) and a regular speed tempo before advancing to more strenuous and technically demanding training protocols involving higher loads or extreme tempos.

Aerobics, which are the lowest load exercise type, and therefore do not involve lactic acid accumulation, are good for preparing the brain for the dopamine depleting effects of strenuous training, I refer to Polyarticular (multi-joint) Aerobics as **Neurogenic Warmups** [See: Motor Units, Muscle Contraction, & Neuromuscular Junctions]. Ideally Neurogenic Warmups will be performed as pre-workout muscle-specific aerobics, such as treadmill walking, or light recumbent bike work before performing your resistance training warmups, or if you choose you may perform your Neurogenic Warmups with another group of muscles. Remember, in the end these are aerobics for the mind, not the muscles, but the muscles will benefit from the low intensity work.

If you do not have the mental energy to perform lactic acid warmups, consider lifting an even lighter weight such as 1-2% your 1RM, and performing sets of a hundred slightly slower, regular-speed repetitions, you don't have to accumulate lactic acid in a muscle for it to be considered warmup, the primary point is hyperemia, and the resultant very high volume contraction-induced molecular anabolic sensitization.

Because thorough and effective resistance training warmups require concentration and are often highly technical they can be difficult to perform when you have a full time job, a physically demanding job, are psychologically stressed, or are physiologically sickly, as

you may lack the energetic brainpower necessary to perform them. In these sorts of scenarios, the best remedy will be enhancing your Inhibitory Control before the workout, you can do this in three ways; The first is to engage in 60-Minutes of Steady-State Cardio at 60% Max Heart Rate (See: ARCS, Cardio, Injuries, & Antagonist Muscle Activation), the second is to enhance Norepinephrine release through drug use or an OTC ergogenic, and the third is to take an hour long nap. If you choose to avoid warmups or to hasten them, even if it saves you time and energy, you will be making a grievous mistake that will present itself later in life, most especially if you are not on steroids, for low load training not only enhances myogenesis, but it rehabilitates injured muscles and tendons indirectly by promoting angiogenesis and protects joints and cartilage from degeneration. Furthermore, lifting low loads is the most sustainable way to train throughout human lifespan, whether an individual is well fed or under fed, well rested or overtired, young or old, and injury-free or injured, you can skip your high intensity or high load workouts, but you should never skip your warmups.

Do understand there is a difference between **Lactic Acid Failure** during an exercise, and **Motor Unit Failure**: The former is *volume (time) x pain threshold* whereas the latter is *volume (time) x CNS-Neurotransmitter threshold*. You primarily want to train your warmup exercises to Lactic Acid Failure (or Hyperemia) if possible during each set which requires lighter weights and higher repetitions (30-80), contrary to the typical warmups performed by gymgoers involving heavier weights and lower repetitions (5-20) leading to *Motor Unit Failure*, which is simply moderate load strength training. The exception to this explanation is Quarter Reps, which often will result in Motor Unit Failure each set, even with very low loads, because you will be training the weakest and least conditioned parts of your muscles, you will have trouble maintaining perfect form during longer sets, and experience rapid neuro-technical fatigue (technical exercise-induced neurotransmitter depletion).

In closing, I will reinstate that Warmup Exercises do not need to result in the accumulation of lactic acid to be considered effective, such that if you walk on a treadmill at a slow pace before sprinting or do six hundred biceps curl repetitions with 1/4th pound microplates before pyramiding up with singles to a barbell biceps curl 1RM PR you are still warming up your muscles, this of course is considered Aerobics, which when performed through compound movements is extremely beneficial for preparing the brain for neurotransmitter exhausting exercise [See: Motor Units, Muscle Contraction, & Neuromuscular Junctions].

Two muscles tend to be overtrained on a weekly basis in both athletic and sedentary individuals; The Biceps, and the lower Hamstrings / Meniscus. You should warmup these muscles with 2-4 Minutes of AMRAP 1-2LB Biceps curls and 2-4 Minutes of Resistance Band Lying Ham Extensions, or Ankle Weight Quarter Rep Standing Hamstring Extensions every morning to overtraining during daily work and home life. Think about

all the objects you pick up on a daily basis, and how far you walk, these muscles are consistently trained through unconscious exercise *every single day*.

Ideally, if you have the time in your day, you should first engage in the lightest form of cardio machine aerobics (which are microrepetitions), followed by Targeted Warmup Exercises focused on hyperemia or lactic acid accumulation, an example of this would look like this:

<u>Squat Day (Shortened Example only)</u>

↓ Neurogenic / Aerobic Warmups:
1. Thirty Minutes Light Treadmill walking.
2. Thirty Minutes Low Level Recumbent Bike Cycling.

OR

1. Sixty Minutes Varied Elevation Hike.

↓ Lactic Acid Warmups:
1. Leg Curls.
2. Hamstring Ext.
3. Floor Adductor Ext.
4. Floor Abductor Ext.
5. Bodyweight Heel Raises.
6. Heels Elevated Bodyweight Squats.
7. Heels Elevated Bodyweight Deadlifts.

↓ Working Sets:
Pyramiding Overload Barbell Squats.
Pyramiding Overload Barbell Deadlifts.

[1] "<>Purpose: This study assessed the influence of an acute aerobic exercise bout on molecular responses to subsequent resistance exercise (RE). Methods: Nine physically active men performed a 45-min one-legged cycle ergometry exercise and 4 × 7 maximal concentric-eccentric knee extensions for each leg 6 h later. Thus, one limb was subjected to aerobic and resistance exercise (AE+RE), and the contralateral limb to resistance exercise (RE) only. Knee extensor peak power was determined. Biopsies were obtained from the m vastus lateralis before (PRE) and 15 min (POST1) and 3 h after RE. Analysis determined glycogen content, mRNA levels (vascular endothelial growth factor, peroxisome proliferator-activated receptor-γ coactivator-1, muscle RING-finger protein-1, atrogin-1, myostatin), and phosphorylated proteins (mammalian target of rapamycin, p70S6 kinase, ribosomal protein S6, eukaryotic elongation factor 2).
<>Results: Peak power was similar in AE + RE and RE. After RE, the time course of glycogen utilization and protein signaling was similar across legs. However, phosphorylation of mammalian target of rapamycin and p70S6 kinase was elevated in AE + RE versus RE (main effect, $P < 0.05$). Vascular endothelial growth factor and peroxisome proliferator-activated receptor-γ coactivator-1 were higher in AE + RE than

in RE at PRE and POST1 ($P < 0.05$). Myostatin was lower in AE + RE versus RE at PRE and POST1 ($P < 0.05$) and downregulated after resistance exercise only. Atrogin-1 was higher in AE + RE than in RE at PRE and POST1 ($P < 0.05$) and decreased after RE in AE + RE. Muscle RING-finger protein-1 was similar across legs. No difference for any marker was evident 3 h after RE. Conclusions: These results suggest that acute aerobic exercise alters molecular events regulating muscle protein turnover during the early recovery period from subsequent RE."[495]

UPPER-BODY WARMUPS

("Band" = Inexpensive Resistance Bands with Handles)
1. PRESSING: Incline 2LB Dbell Quarter Rep Bench Presses (All Angles, All Wrist Positions) > Incline Empty Light weight Hex Bar Quarter / Partial Rep Presses (Total weight 13LB) (All Angles, All Wrist Positions) > Incline 2LB Dbell Pronated / Supinated JM Presses.
2. ROWING: Incline 2LB Dbell Prone Rows (All Angles, All Wrist Positions).
3. CHEST / ARMS: 2LB Dbell Quarter Rep Flat Bench Chest Flies > 2LB Dbell Biceps Curls (All Angles, All Wrist Positions) > Band Wrist Pronation + Supination > 2LB Dbell Triceps Ext (All Angles, All Wrist Positions)> Band w/Handles Finger Curls > Band Wrist Curls > Band Thumb Ext > Band Ulnar / Radial Deviation Ext > Rice Bucket Grip Training (Squeezing, Finger Splaying, Hand Clamping > Wrist Pronation – Supination – Wrist / Finger Extension / Flexion)
4. SHOULDERS: 2LB Dbell Quarter Rep Side Laterals > Leaning 2LB Dbell Quarter Rep Side Laterals > 2LB Dbell Rotator Cuff Adduction Ext (Elbows pinned to Obliques) > Upwards Shoulder Rotations (Martin Licis Style) > 2LB Dbell Shrugs (All Angles) > 2LB Dbell Upright Rows > 2LB Dbell Bent-Over Horizontal Flies.
5. FINISHERS: Quarter Rep Wall-Pushups (Low volume, no lockouts, slower tempo, multiple grip widths / wrist orientations).

LOWER-BODY WARMUPS

1. CORE / GROIN: Crunches > Floor Leg Lifts > Floor Adductor / Abductors Ext > 2LB Dbell Standing Side Bends > Eccentric Decline Bench Sit-ups.
2. HAMS / BACK: Quarter Rep Lying Ham Ext > Seated Bodyweight Atlas (Bench) Deadlifts > Quarter Rep Bodyweight Deadlifts (Close / Wide Stance, Right / Left Leaning) > Quarter Rep Toes Elevated Bodyweight Deadlifts > Bench Bodyweight Reverse Hypers.
3. QUADS / CALVES: Quarter Rep Bodyweight Squats (Close / Wide Stance) > Quarter Rep Bodyweight Heel Elevated Squats (Low Volume) > Quarter Rep Ballerina (tippy toe) Squats (Very Low Volume).

4. NECK / CALVES: Bench Front Neck Ext > Lying-Stomach Bench Rear Neck Ext > Bodyweight Heel Raises > Band w/Handle attached to shoes Tibialis Ext.
[To understand Quarter / Middle / Partial Reps, See: Exercise Range of Motion Definitions]

!!! Remember, Warmups should be very light weight, do not assume a 2LB or 3LB dumbbell is too "light" for you when you cannot perform dozens of controlled repetitions in one set with them without moving the weights explosively, which is a form of Unconscious Lifting, and is cheating the time-under-tension. **!!!**

Tendon Injuries

The obvious first step to promoting tendon regeneration is avoiding strong Anti-Inflammatory supplements and focusing on promoting tendon angiogenesis & collagen synthesis (+TGF-b). Avoiding explosive exercises is advisable. Ascorbic Acid and Glycine will be your greatest friends when your tendons become inflamed or injured. Local Vibration Therapy will be a therapeutic modality to potentially promote tendon regeneration, or at the very least to promote localized blood flow.

[A] Ascorbic Acid.

"<>Numerous studies from our laboratory have defined aspects of the repair process in a lacerated flexor tendon model, both in vivo and in vitro. Inherent in the development of a viable tissue or cell culture model system is the definition of the optimal media environment. Since our laboratory investigations of in vitro flexor tendon repair encompass the formation of numerous extracellular matrix proteins, we have defined the optimal level of ascorbic acid with which to study the tendon wound healing process. <>The ascorbic acid requirement for proline and lysine hydroxylase activity during collagen biosynthesis is well known, and the importance of this vitamin for matrix proteoglycan synthesis more recently has been appreciated. This report describes the effect of several levels of ascorbic acid on 3H-thymidine incorporation, collagen and noncollagen protein synthesis, and glucose utilization and lactate production. Profundus flexor tendon segments were obtained from young adult New Zealand white rabbits and maintained in organ culture for periods of 1, 2, or 3 weeks. Ascorbic acid concentrations ranged from 50 to 300 micrograms/ml and were added fresh at each 48-h media change. Tendon protein synthesis, glucose metabolism, and cell permeability/viability were significantly correlated with the level of ascorbic acid in the culture medium. <>The results suggest that ascorbic acid levels in excess of the traditional 50 micrograms/ml are necessary to optimally maintain flexor tendons from adult animals in organ culture with 48-h media and ascorbate changes. Additionally, it may be necessary

to determine the precise ascorbic acid requirement for individual tissues, since the specific tissue/cell and species requirement for ascorbate may vary."[496]

[B] Glycine.

"<>Tendinopathy of the Achilles tendon is a clinical problem that motivates the scientific community to search for treatments that assist in restoring its functional properties. Glycine has broad biological effects, acting as a modulator of the inflammatory cascade, and is the predominant amino acid in collagen. A 5% glycine diet provided beneficial effects against toxicity and inflammation since glycine may restructure the collagen molecules faster due to its broad anti-inflammatory effects. <>The purpose was analyzing the effects of a 5% glycine diet in rats as a treatment for the inflammatory process. The experimental groups were as follows: C (control group), G1 and G3 (inflammatory group), and G2 and G4 (glycine+inflammatory group). G1 and G2 were euthanized 8 days following injury, and G3 and G4 were euthanized 22 days following injury. The concentrations of hydroxyproline, non-collagenous proteins, and glycosaminoglycans, as well as the activity of MMP-2 and -9 were analyzed. Biomechanical and morphological tests were employed. Higher concentrations of hydroxyproline and glycosaminoglycans were found in G4 and an increased activity of MMP-2 was found in G2. Higher birefringence was noted in group G2. The biomechanical results indicated that the tendon was more resistant to loading to rupture upon treatment with a glycine diet in group G4. <>Glycine induced the synthesis of important components of the tendon. A rapid remodeling was noted when compared with the inflamed-only groups. These data suggest that glycine may be a beneficial supplement for individuals with inflammation of the Achilles tendon."[497]

[C] Isometric Training: This form of training has been shown to increase tendon stiffness and elasticity (Young's Modulus)[1]. Increased tendon stiffness is a necessity for strength and explosive athletes, as it allows greater and faster force transmission during muscle contraction and is essential for the adaptation tendons experience during the development of physical strength. Furthermore, and quite impressively, Isometric Training appears to enhance tendon healing directly by promoting Tendon Hyperemia (Blood Flow), even when lower intensity Isometrics are performed (50% Maximal Voluntary Isometric Contraction x 5-Seconds, or better explained as 50% Maximal Force) [2].

[1] "<>The present study aimed to investigate the effect of isometric training on the elasticity of human tendon structures. Eight subjects completed 12 wk (4 days/wk) of isometric training that consisted of unilateral knee extension at 70% of maximal voluntary contraction (MVC) for 20 s per set (4 sets/day). Before and after training, the elongation of the tendon structures in the vastus lateralis muscle was directly measured using ultrasonography while the subjects performed ramp isometric knee extension up to MVC. The relationship between the estimated muscle force and tendon elongation (L)

was fitted to a linear regression, the slope of which was defined as stiffness of the tendon structures.
<>The training increased significantly the volume (7.6+/-4.3%) and MVC torque (33.9+/-14.4%) of quadriceps femoris muscle. The L values at force production levels beyond 550 N were significantly shorter after training. The stiffness increased significantly from 67.5+/-21.3 to 106.2+/-33.4 N/mm. Furthermore, the training significantly increased the rate of torque development (35.8 +/- 20.4%) and decreased electromechanical delay (-18.4+/-3.8%).
<>Thus, the present results indicate that isometric training increases the stiffness and Young's modulus of human tendon structures as well as muscle strength and size. This change in the tendon structures would be assumed to be an advantage for increasing the rate of torque development and shortening the electromechanical delay."[497.1]

[2] "<>Acute increases in tendon blood flow and oxygenation after stress (i.e., hyperemic response) can enhance tendon recovery. While loading intensity is a fundamental part of resistance training programs, its effects on tendon's hyperemic response are unknown. This study aimed to compare acute changes in total (total hemoglobin [THb]) and oxygenated hemoglobin (HbO_2) concentrations in the patellar tendon after isometric exercise at different intensities. Thirteen participants performed 8 (5 s) isometric knee extensions at 25%, 50%, and 75% maximal load (maximal voluntarily isometric contraction [MVIC]), separated by 20 min recovery, prescribed in randomized and counterbalanced order. Changes in patellar tendon THb, HbO_2 and deoxygenated hemoglobin (HHb) in response to exercise at each intensity were measured using near-infrared spectroscopy.
<>Post-exercise, HbO_2 increased with 50% ($\eta 2p\eta p2 = 0.305$, $f = 5.26$, $p < 0.01$) and 75% ($\eta 2p\eta p2 = 0.245$, $f = 4.56$, $p < 0.01$) but not 25% ($\eta 2p\eta p2 = 0.088$, $f = 1.16$, $p = 0.339$) MVIC, while THb increased in 50% ($\eta 2p\eta p2 = 0.305$, $f = 5.26$, $p = 0.01$) but not 25% ($\eta 2p\eta p2 = 0.067$, $f = 0.865$, $p = 0.51$) or 75% ($\eta 2p\eta p2 = 0.126$, $f = 1.729$, $p = 0.14$) MVIC.
<>Additionally, increasing load from 25% to 50% MVIC resulted in greater THb ($f = 2.459$, $p = 0.43$), HbO_2 ($f = 3.389$, $p = 0.13$) and HHb ($f = 0.320$, $p = 0.01$) post-exercise responses, but no differences were observed between 50% and 75% MVIC (THb: $f = 0.748$, $p = 0.59$; HbO_2 : $f = 0.825$, $p = 0.54$; HHb: $f = 0.713$, $p = 0.62$).
<>Our results suggest there is a loading threshold at ~50% MVIC at which the tendon hyperemic response is fully achieved. Training above this intensity is not expected to provide any additional change to the tendon microvascular response. Therefore, moderate loading seems to be sufficient to fully elicit the patellar tendon hyperemic response that's believed to stimulate tendon healing."[497.2]

Superslow Training for Tendon Regeneration and Growth: Although this is subjectively only my experience as of writing this, having numerous tendon injuries

myself from years of unnecessary overtraining, inspired by the training protocols and training methods of enhanced athletes, I find it to be the best training style to strengthen tendons, especially when the time-under-tension, primarily from 0-25% ROM, is a minimum of 6+ Seconds. Don't go above 50% your Superslow 1RM.

[See: Pro-Inflammation Modalities: Local Vibration Therapy]

[See: AGE Inhibitors: Alpha-lipoic Acid]

Novel Prescription Myogenic / Neurotrophic Chemicals

Many prescriptions have off-label uses that are unknown to modern medical professionals. And although some of these prescriptions have potent beneficial effects on muscles or the brain, or other aspects of human physiology, they do carry with them many insidious toxic side effects (primarily psychotropics).

Regardless, it is important to be aware of the benefits of some commonly prescribed drugs, so that in the case you are prescribed a similar class of drug, you may choose to request one from your doctor that aligns more with your physical or neurological goals.

Valproic Acid

Valproic Acid through HDAC Inhibition promotes muscle hypertrophy.

"<>The tight interaction between genomic DNA and histones, which normally represses gene transcription, can be relaxed by histone acetylation. This loosening of the DNA-histone complex is important for selective gene activation during stem cell differentiation. Histone acetylation may be increased through the application of histone deacetylase inhibitors at the early stages of differentiation to modulate lineage commitment. We examined the effects of the histone deacetylase inhibitor valproic acid on the differentiation of pluripotent stem cells into skeletal myocytes. Our data demonstrated that valproic acid can act in concert with retinoic acid to enhance the commitment of stem cells into the skeletal myocyte lineage reinforcing the notion that histone acetylation is important for skeletal myogenesis. Thus, using a combination of small molecules to exploit different signaling pathways pertaining to specific gene programs will allow for modulation of lineage specification and stem cell differentiation in potential cell-based therapies."[498]

ACE Inhibitors (Not AGE)

Ace Inhibitors appear to enhance circulating IGF-1.

"<>Objectives: The present study evaluates the effects of a 6-month treatment with an ACE-inhibitor (ie, fosinopril) on serum concentrations of total IGF-1 and IGF binding

protein (IGFBP)-3 in older adults at high risk for cardiovascular disease. Measurements: Serum concentrations of total IGF-1 and IGFBP-3 were measured in 100 participants of the TRAIN study at baseline, 6-month and 12-month follow-up visits. Differences in total IGF-1 and IGFBP-3 concentrations were assessed using two-sided paired tests. <>Results: The mean age of participants (47% women) was 66.5 (standard deviation 7.2) years. Serum concentrations of total IGF-1 were significantly higher after 6-month treatment with fosinopril compared to placebo (203.73 ng/mL vs 194.24 ng/mL; p=0.02): After ACE-inhibitor intervention, significantly higher serum IGFBP-3 concentrations compared to controls (4308.81 ng/mL vs 4086.93 ng/mL; p=0.03) were also reported. Conclusions: A six-month treatment with fosinopril increases systemic levels of total IGF-1 and IGFBP-3 in older adults with high cardiovascular risk profile. This may represent a potential biological explanation to the beneficial effects of ACE-inhibition on stroke, ischemic heart disease and insulin resistance."[499]

Fluoxetine

I am including research on this SSRI not because I believe it is a good psychotropic, but primarily because it displays the myogenic benefits of Serotonin, the future potential for mass market Ceramide Inhibitors, and the pernicious and strangely specific florae toxicity of this popular drug.

[A] Fluoxetine facilitates muscle strength (slow twitch fiber growth).

"<>Aim: Fluoxetine, one of the first newer SSRI antidepressant, is an extremely popular treatment for depression that could improve mental health problems. Many recent studies have suggested that SSRI have potential beneficial effects on skeletal muscle tissue. <>Main method: We evaluated the potential beneficial effects of oral fluoxetine (18 mg/kg/day for 6 weeks) on muscle performance, after 6 weeks of physical exercise on treadmill. Male mice were randomly assigned to four groups (n = 12 per group) for treatment. Each group received treatment with following specifications: 1) no exercise with vehicle treatment (SED-S); 2) no exercise with fluoxetine treatment (SED-F); 3) exercise with vehicle treatment (EX-S); and 4) exercise with fluoxetine treatment (EX-F). Exercise performances were assessed based on the exhaustive running time and forelimb grip strength, anxious behavior by elevated plus-maze and open-field tests. Mitochondrial enzymes activity and ROS production were measured in the gastrocnemius and soleus muscles.
<>Key finding: Fluoxetine treatment had a significant effect on maximal aerobic capacity in mice without exercise, but more significant effects on gripping strength and anxiety when combined with exercise training, e.g. increased strength and decreased anxiety."[500]

[B] Fluoxetine reduces neuronal Ceramide levels.

"<>The antidepressants amitriptyline, a tricyclic drug, and fluoxetine, a selective serotonin reuptake inhibitor, inhibited ASM activity in cultured neurons at therapeutic plasma concentrations recommended for patients with major depression. Treatment of wild-type (WT) mice with amitriptyline or fluoxetine dose dependently reduced hippocampal Asm activity and protein levels."[501]

[C] Although a majority of SSRI's are "dirty drugs", and carry with them deleterious neurotoxic consequences, it is possible that locally administered (intramuscular) Serotonin would enhance myogenesis.

"<>Myostatin (MSTN), a member of the transforming growth factor beta family, negatively regulates skeletal muscle mass. Deletion of the Mstn gene results in increased muscle mass. Also, Mstn-/- mice and mice expressing a dominant negative MSTN receptor (activin receptor type IIB, ACVR2B) show decreased adipose tissue. Mstn-/- mice fed a high fat diet gain less weight, have improved glucose tolerance and are more sensitive to insulin when compared to wild type controls. We are interested in characterizing molecules that may be downstream of MSTN signaling. <>We identified serotonin as a potential molecule that may interact with MSTN in skeletal muscle. Serotonin is thought to regulate both metabolism and cardiac hypertrophy, but it is not clear if serotonin is synthesized and functions in the skeletal muscle. We hypothesize that serotonin regulates skeletal muscle mass and metabolism, and the serotonin and myostatin pathways interact with each other. <>Expression of tryptophan hydroxylase 1 (Tph1), the enzyme that catalyzes the rate limiting step in serotonin synthesis was significantly increased by microarray in transgenic mice and by RT-qPCR in mice receiving the soluble receptor. Serotonin significantly promoted longitudinal growth of skeletal muscle fibers in vitro. Increased branching, differentiation and fusion of myoblasts into myotubes were also observed. Serotonin was detectable in muscle from transgenic mice and in L6 myoblasts and myotubes."[502]

[C] Fluoxetine reduces Lactobacilli populations in the human gut which will surely accompany cognitive perturbations over time in human use scenarios, as evidenced by the fact the lab mice began to display signs of anxiogenesis during the trial. Do you not find it eerily strange that a commonly prescribed psychotropic for promoting "happiness" or reducing depressive thoughts, actually harms our guts, which play such a vital role in regulating our mood, memory, and intelligence? How many other prescription psychotropics destroy our microbiome, and are these dysbiosis promoting effects biomedically unintentional, or instead biomedically premeditated?

"<>Background: Depression and major depressive disorder affect 25% of the population. First line treatment utilizing selective serotonin reuptake inhibitors (SSRIs) have met with limited success due to well-recognized negative side effects which include weight gain or loss. This inability to control unwanted side effects often result in patients

stopping their antidepressant medications. The mechanisms underlying the failure of SSRIs are incompletely understood.
<>Methods: Male CF-1 mice (5 weeks of age, *N* = 10 per group) were per orally administered fluoxetine (20 mg per kg body weight) or diluent daily for 29 days. During this time fecal specimens were collected at three defined time points (0, 15 and 29 days). At the conclusion of the 29-day dosing regimen, animals were subjected to two behavioral assessments. For bacterial identification of the microbiota, 16S rRNA gene sequencing was performed on 60 fecal specimens (three specimens per mouse time course, *N* = 20 mice) using Illumina MiSeq. Analysis of community sequence data was done using mothur and LEfSe bioinformatic software packages.
<>Results: Daily per oral administration of fluoxetine for 29 days to male mice resulted in a significant, time dependent, alteration in microbial communities accompanying changes in body weight. The calculated species richness and diversity indicators of the murine fecal microbial communities were inconsistent and not significantly different between the groups. Among the phylotypes decreased in abundance due to fluoxetine administration were *Lactobacillus johnsonii* and *Bacteroidales S24-7* which belong to phyla associated with regulation of body mass. The observed changes in body weight due to fluoxetine administration mimicked the dramatic shifts in weight gain/loss that has been observed in humans. Further, at the conclusion of the 29-day dosing regimen fluoxetine-dosed animals evidenced a mild anxiogenic-like behavior.
<>Discussion: We report that the most widely used antidepressant, fluoxetine, which is an SSRI-type drug, results in the selective depletion of gut microbiota, specifically the Lactobacilli which are involved in the regulation of body weight. Concomitantly, fluoxetine administration increases the abundance of phylotypes related to dysbiosis. Since Lactobacilli have been previously shown to possess a known biogenic amine transporter that regulates the uptake of fluoxetine, it is proposed that a microbial endocrinology-based mechanistic pathway is responsible for the ability of SSRIs to selectively negatively impact beneficial microbiota. The results of this study therefore suggest that the negative clinical side effects due to fluoxetine administration may be due to alterations in gut microbiota. Further, the data also suggests that supplementation of bacterial genera directly affected by fluoxetine administration may prove useful in ameliorating some of the well-known side effects of chronic fluoxetine administration such as weight alterations.[502.0]

Fluvoxamine

Not to be confused with Fluoxetine, Fluvoxamine is an SSRI that appears to be the most effective and safest antidepressant due to having an affinity to agonize the Sigma-1 Receptors, which promote Nerve Growth Factor expression in the brain to promote neuritogenesis. Of course, like all SSRI's, and many psychotropic pharmaceuticals, it will cause weight gain, or other deleterious physiological side effects, which is why it should

be only used as a last option, and never combined with Caffeine as it interacts with liver Cytochromes.

“<>Background: Selective serotonin reuptake inhibitors (SSRIs) have been widely used and are a major therapeutic advance in psychopharmacology. However, their pharmacology is quite heterogeneous. The SSRI fluvoxamine, with sigma-1 receptor agonism, is shown to potentiate nerve-growth factor (NGF)-induced neurite outgrowth in PC 12 cells. However, the precise cellular and molecular mechanisms underlying potentiation by fluvoxamine are not fully understood. In this study, we examined the roles of cellular signaling pathways in the potentiation of NGF-induced neurite outgrowth by fluvoxamine and sigma-1 receptor agonists.
<>Methods and findings: The effects of three SSRIs (fluvoxamine, sertraline, paroxetine) and three sigma-1 receptor agonists (SA4503, 4-phenyl-1-(4-phenylbutyl) piperidine (PPBP), and dehydroepiandrosterone (DHEA)-sulfate) on NGF-induced neurite outgrowth in PC12 cells were examined. Also examined were the effects of the sigma-1 receptor antagonist NE-100, inositol 1,4,5-triphosphate (IP(3)) receptor antagonist, and specific inhibitors of signaling pathways in the potentiation of NGF-induced neurite outgrowth by selective sigma-1 receptor agonist SA4503. Fluvoxamine (but not sertraline or paroxetine) and the sigma-1 receptor agonists SA4503, PPBP, and DHEA-sulfate significantly potentiated NGF-induced neurite outgrowth in PC12 cells in a concentration-dependent manner.
<>The potentiation by fluvoxamine and the three sigma-1 receptor agonists was blocked by co-administration of the selective sigma-1 receptor antagonist NE-100, suggesting that sigma-1 receptors play a role in blocking the enhancement of NGF-induced neurite outgrowth. Moreover, the potentiation by SA4503 was blocked by co-administration of the IP(3) receptor antagonist xestospongin C. In addition, the specific inhibitors of phospholipase C (PLC-gamma), phosphatidylinositol 3-kinase (PI3K), p38MAPK, c-Jun N-terminal kinase (JNK), and the Ras/Raf/mitogen-activated protein kinase (MAPK) signaling pathways blocked the potentiation of NGF-induced neurite outgrowth by SA4503.
<>Conclusion: These findings suggest that stimulation of sigma-1 receptors and subsequent interaction with IP(3) receptors, PLC-gamma, PI3K, p38MAPK, JNK, and the Ras/Raf/MAPK signaling pathways are involved in the mechanisms of action of sigma-1 receptor agonists such as fluvoxamine and SA4503.”[502.1]

Atomoxetine

Strattera is my favorite prescription drug because increasing Norepinephrine is one of the safest ways to play with neurochemistry, whereas playing with dopamine or serotonin levels is far more dangerous to mood and memory. The issue with Atomoxetine is that it is an NMDAr antagonist in the prefrontal cortex, which means although its use may make you stronger, it will reduce to a certain extent your ability to form memories, and because

Norepinephrine is associated with the stress response, it will enhance anxiety if you are prone to it, or if you are currently experience chronic psychological stress. Atomoxetine has been shown to prevent cortisol-induced muscle atrophy.

"<>Skeletal muscle atrophy remains a clinical problem in numerous pathologic conditions. β2-Adrenergic receptor agonists, such as formoterol, can induce mitochondrial biogenesis (MB) to prevent such atrophy. Additionally, atomoxetine, an FDA-approved norepinephrine reuptake inhibitor, was positive in a cellular assay for MB. We used a mouse model of dexamethasone-induced skeletal muscle atrophy to investigate the potential role of atomoxetine and formoterol to prevent muscle mass loss. Mice were administered dexamethasone once daily in the presence or absence of formoterol (0.3 mg/kg), atomoxetine (0.1 mg/kg), or sterile saline. Animals were euthanized at 8, 16, and 24 hours or 8 days later. Gastrocnemius muscle weights, changes in mRNA and protein expression of peroxisome proliferator-activated receptor-γ coactivator-1 α (PGC-1α) isoforms, ATP synthase β, cytochrome c oxidase subunit I, NADH dehydrogenase (ubiquinone) 1 β subcomplex, 8, ND1, insulin-like growth factor 1 (IGF-1), myostatin, muscle Ring-finger protein-1 (muscle atrophy), phosphorylated forkhead box protein O 3a (p-FoxO3a), Akt, mammalian target of rapamycin (mTOR), and ribosomal protein S6 (rp-S6; muscle hypertrophy) in naive and muscle-atrophied mice were measured.
<>Atomoxetine increased p-mTOR 24 hours after treatment in naïve mice but did not change any other biomarkers. Formoterol robustly activated the PGC-1α-4-IGF1-Akt-mTOR-rp-S6 pathway and increased p-FoxO3a as early as 8 hours and repressed myostatin at 16 hours. In contrast to what was observed with acute treatment, chronic treatment (7 days) with atomoxetine increased p-Akt and p-FoxO3a, and sustained PGC-1α expression and skeletal muscle mass in dexamethasone-treated mice, in a manner comparable to formoterol. In conclusion, chronic treatment with a low dose of atomoxetine prevented dexamethasone-induced skeletal muscle wasting and supports a potential role in preventing muscle atrophy."[503]

Prazosin

Prazosin promotes skeletal muscle angiogenesis.

"<>The increase of wall shear stress in capillaries by oral administration of the alpha1-adrenergic receptor antagonist prazosin induces angiogenesis in skeletal muscles. Because endothelial nitric oxide synthase (eNOS) is upregulated in response to elevated wall shear stress, we investigated the relevance of eNOS for prazosin-induced angiogenesis in skeletal muscles. Prazosin and/or the NOS inhibitor Nomega-nitro-L-arginine methyl ester (L-NAME) were given to C57BL/6 wild-type mice and eNOS-knockout mice for 14 days. The capillary-to-fiber (C/F) ratio and capillary density (CD; no. of capillaries/mm2) were determined in frozen sections from extensor digitorum

longus (EDL) muscles of these mice. Immunoblotting was performed to quantify eNOS expression in endothelial cells isolated from skeletal muscles, whereas VEGF (after precipitation with heparin-agarose) and neuronal NOS (nNOS) concentrations were determined in EDL solubilizates.
<>In EDL muscles of C57BL/6 mice treated for 14 days, the C/F ratio was 28% higher after prazosin administration and 11% higher after prazosin and L-NAME feeding, whereas the CD increased by 21 and 13%, respectively. The C/F ratio was highest after day 4 of prazosin treatment and decreased gradually to almost constant values after day 8. Prazosin administration led to elevation of eNOS expression. VEGF levels were lowest at day 4, whereas nNOS values decreased after day 8. In EDL muscles of eNOS-knockout mice, no significant changes in C/F ratio, CD, or VEGF and nNOS expression were observed in response to prazosin administration. Our data suggest that the presence of eNOS is essential for prazosin-induced angiogenesis in skeletal muscle, albeit other signaling molecules might partially compensate for or contribute to this angiogenic activity. Furthermore, subsequent remodeling of the capillary system accompanied by sequential downregulation of VEGF and nNOS in skeletal muscle fibers characterizes shear stress-dependent angiogenesis."[503.1]

Lipitor

A common drug prescribed for cardiovascular disease promotes neurogenesis by way of VEGF expression.

"<>Molecular mechanisms underlying the role of statins in the induction of brain plasticity and subsequent improvement of neurologic outcome after treatment of stroke have not been adequately investigated. Here, we use both in vivo and in vitro studies to investigate the potential roles of two prominent factors, vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF), in mediating brain plasticity after treatment of stroke with atorvastatin. Treatment of stroke in adult mice with atorvastatin daily for 14 days, starting at 24 hours after MCAO, shows significant improvement in functional recovery compared with control animals. <>Atorvastatin increases VEGF, VEGFR2 and BDNF expression in the ischemic border. Numbers of migrating neurons, developmental neurons and synaptophysin-positive cells as well as indices of angiogenesis were significantly increased in the atorvastatin treatment group, compared with controls. In addition, atorvastatin significantly increased brain subventricular zone (SVZ) explant cell migration in vitro. Anti-BDNF antibody significantly inhibited atorvastatin-induced SVZ explant cell migration, indicating a prominent role for BDNF in progenitor cell migration. Mouse brain endothelial cell culture expression of BDNF and VEGFR2 was significantly increased in atorvastatin-treated cells compared with control cells. Inhibition of VEGFR2 significantly decreased expression of BDNF in brain endothelial cells. These data indicate that atorvastatin promotes angiogenesis, brain plasticity and enhances functional recovery after stroke. In

addition, VEGF, VEGFR2 and BDNF likely contribute to these restorative processes."[503.2]

Mirabegron

Mirabegron is a medication commonly prescribed for overactive bladder issues and is relatively easy to convince a doctor to prescribe, especially if you are a bodybuilder, or strength athlete, and already suffer from an overactive nocturnal polyuria. Through agonism of Beta-3 adrenergic receptors, it appears that Mirabegron is capable of promoting lipolysis, the browning of white fat, the slow twitch phenotype, and possibly myogenesis through increased PGC1a expression.

"<>BACKGROUND: Beige adipose tissue is associated with improved glucose homeostasis in mice. Adipose tissue contains β3-adrenergic receptors (β3-ARs), and this study was intended to determine whether the treatment of obese, insulin-resistant humans with the β3-AR agonist mirabegron, which stimulates beige adipose formation in subcutaneous white adipose tissue (SC WAT), would induce other beneficial changes in fat and muscle and improve metabolic homeostasis.
<>METHODS: Before and after β3-AR agonist treatment, oral glucose tolerance tests and euglycemic clamps were performed, and histochemical analysis and gene expression profiling were performed on fat and muscle biopsies. PET-CT scans quantified brown adipose tissue volume and activity, and we conducted in vitro studies with primary cultures of differentiated human adipocytes and muscle.
<>RESULTS: The clinical effects of mirabegron treatment included improved oral glucose tolerance ($P < 0.01$), reduced hemoglobin A1c levels ($P = 0.01$), and improved insulin sensitivity ($P = 0.03$) and β cell function ($P = 0.01$). In SC WAT, mirabegron treatment stimulated lipolysis, reduced fibrotic gene expression, and increased alternatively activated macrophages. Subjects with the most SC WAT beiging showed the greatest improvement in β cell function. In skeletal muscle, mirabegron reduced triglycerides, increased the expression of PPARγ coactivator 1 α (PGC1A) ($P < 0.05$), and increased type I fibers ($P < 0.01$). Conditioned media from adipocytes treated with mirabegron stimulated muscle fiber PGC1A expression in vitro ($P < 0.001$).
<>CONCLUSION: Mirabegron treatment substantially improved multiple measures of glucose homeostasis in obese, insulin-resistant humans. Since β cells and skeletal muscle do not express β3-ARs, these data suggest that the beiging of SC WAT by mirabegron reduces adipose tissue dysfunction, which enhances muscle oxidative capacity and improves β cell function."[503.3]

Stretching

Stretching has direct benefits to tendons, it could hypothetically also protect against tendon injury by enhancing muscle growth in the muscle tissue near the tendons, thus contributing to less tendon load and a reduced risk of injury, conversely stretching on a *high frequency workout* protocol will increase your risk for injury by damaging the muscle nearest to your tendons. I suggest saving your stretching for the last day before detraining or deloading the day after your final and most intense workout, spending hours progressively stretching your muscles with various stretching exercises, then letting the muscles and tendons recover for two weeks or more before lifting anything above moderate loads, I refer to this as ***Extreme Stretching***. If you intend on stretching while exercising frequently and intensely, it would be intelligent to reserve it for a Pro-Cycle as it is capable of causing such severe damage to muscle tissue. The idea for stretching the day after an intense training session must be credited to the world record breaking deadlifter Andy Bolton.

If you pursue my ideal idea for Stretching (one intense, long duration, and extremely painful stretching session infrequently performed on an off day: Extreme Stretching), you should consume a good amount of whey isolate and glutamine pre/post-workout, as this should hypothetically accelerate stretch-induced myogenesis. Considering Stretching is considered an exercise, and causes muscle damage, it makes no sense to me not to consume large amounts of fast digesting amino acids during and after Stretching.

Stretching immediately post-workout seems intelligent, but it makes little sense, considering muscle hyperemia will reduce stretch-induced pain signaling, you won't be able to tell how hard or light you are stretching a muscle or tendon, it therefore makes the most sense to stretch when you are "cold", to ensure that you feel the greatest pain signaling and can manipulate and contort your body according to this signaling, to achieve the very best Stretching exercises through feel. Stretching is strangely the only highly damaging exercise that should be performed without warmups.

Finally, if a stretching exercise is not painful to perform, it is not effective towards the promotion of muscle growth as the pain is a clear indication that damage is actively occurring within the muscles and tendons. Those who do not compete in sports and yet stretch multiple times a week, and have extremely impressive flexibility, have either partially or completely nullified the myogenic benefits of Stretching, which is why I suggest taking a long break from Stretching after maximal flexibility has been reached to restore musculoskeletal stiffness, or the *potential for stretch-induced damage*.

I personally prefer to engage in six hours of full body Extreme Stretching (neck, shoulders, pectorals, biceps, forearms, triceps, rear delts, teres, outer lats, hamstrings, quadriceps, & calves) one day every four-five weeks, this gives me a month or more of recovery between stretch sessions, and because I place this full body extremely painful stretch workout the day after my heaviest / hardest workout, it does not interfere with my other programmed workouts, as the following days after my stretch day are detraining,

and the following weeks are lower load, or lower intensity programmed training, whereas if I was to stretch before a workout, or at a much higher frequency, I would be predisposing myself to a muscle or tendon injury, depending on intensely I stretch (clearly stretching *lightly* before each workout will not influence injury risk).

[A] Stretching is only useful as tendon-injury prevention for explosive athletes.

"<>It is generally accepted that increasing the flexibility of a muscle-tendon unit promotes better performances and decreases the number of injuries. Stretching exercises are regularly included in warm-up and cooling-down exercises; however, contradictory findings have been reported in the literature. Several authors have suggested that stretching has a beneficial effect on injury prevention. In contrast, clinical evidence suggesting that stretching before exercise does not prevent injuries has also been reported. Apparently, no scientifically based prescription for stretching exercises exists and no conclusive statements can be made about the relationship of stretching and athletic injuries.
<>Stretching recommendations are clouded by misconceptions and conflicting research reports. We believe that part of these contradictions can be explained by considering the type of sports activity in which an individual is participating. Sports involving bouncing and jumping activities with a high intensity of stretch-shortening cycles (SSCs) [e.g. soccer and football] require a muscle-tendon unit that is compliant enough to store and release the high amount of elastic energy that benefits performance in such sports. If the participants of these sports have an insufficient compliant muscle-tendon unit, the demands in energy absorption and release may rapidly exceed the capacity of the muscle-tendon unit. This may lead to an increased risk for injury of this structure.
<>Consequently, the rationale for injury prevention in these sports is to increase the compliance of the muscle-tendon unit. Recent studies have shown that stretching programmes can significantly influence the viscosity of the tendon and make it significantly more compliant, and when a sport demands SSCs of high intensity, stretching may be important for injury prevention. This conjecture is in agreement with the available scientific clinical evidence from these types of sports activities. In contrast, when the type of sports activity contains low-intensity, or limited SSCs (e.g. jogging, cycling and swimming) there is no need for a very compliant muscle-tendon unit since most of its power generation is a consequence of active (contractile) muscle work that needs to be directly transferred (by the tendon) to the articular system to generate motion.
<>Therefore, stretching (and thus making the tendon more compliant) may not be advantageous. This conjecture is supported by the literature, where strong evidence exists that stretching has no beneficial effect on injury prevention in these sports. If this point of view is used when examining research findings concerning stretching and injuries, the reasons for the contrasting findings in the literature are in many instances resolved."[505]

[B] Even light Stretching enhances MyoD & Myogenin (differentiation).

"<>We stretched medial gastrocnemius muscles in rats under deep anesthesia without applying resistant force within the natural range of motion in order to avoid muscle damage. Passive stretching for 15 min daily within a 1-week period induced the expression of MyoD, myogenin, and embryonic MyHC mRNA. We examined the potential of remote hormonal factor participation. No significant differences were observed between continuous and repetitive unstretched sides, and the control groups showed stretch effects that were restricted to the affected region. This observation demonstrates that remote hormonal factors did not influence our results."[506]

[C] Overload Stretching (progressively increasing the tension load on the muscles i.e., painful stretching) every 72h for around ten days followed by four days of stretching in a row substantially increases muscle hypertrophy, although this effect subsides from day twenty five onward. Although this study is bit complicated to understand, considering the stretching protocol begins with stretching at every 72h mark, until Day-11 where there is 4-days of concurrent stretching, we can understand that there is a point in time where muscle tissue begins to experience breakdown rather than growth, where the muscle cross sectional area "critical size" of muscle tissue has been reached (a hypertrophy plateau). Whether this hypertrophy plateau occurs in humans after three weeks of high frequency training (every 72h, 48h, or 24h), or four weeks, or five weeks is irrelevant, what matters is that deloading and detraining must be incorporated into every high frequency, high load training protocol, ideally at the fourth or fifth week of serious training, whereas if you are only training a muscle once a week with heavy weight, this growth plateau might not be relevant.

Interestingly, this study shows that hypertrophy continues even from Day-11 to Day-16 (where the muscles are stretched everyday), this may give a clue as to the bodies limit of "Squat Everyday", or "Deadlift Everyday", that being four days of destructive high load training before muscle breakdown.

As for mimicking Overload Stretching, it is not very complicated, it should be very painful, and if you require resistance, have a friend or family member add force to your stretching exercises. If you're too flexible to experience pain during the common stretching movements, it may be time to detrain from stretching for a few months unless your chosen sport is explosive, to allow your muscles & tendons a chance to return to a higher level of stiffness.

As an addendum, I am aware Stretch-induced muscle damage is different from contraction-induced muscle damage, but they both result in hypertrophy, and both forms of muscle damage result in plateaus of growth, or at the very least plateaus of early hypertrophy.

"<>Intermittent stretch of the anterior latissimus dorsi (ALD) muscle produces fiber hypertrophy without fiber hyperplasia. This study was undertaken to determine if a progressive increase in load and duration of stretch would induce extremely large muscle

fiber areas or if the fibers would reach a critical size before the onset of fiber hyperplasia. Weights ranging from 10 to 35% of the bird's mass were attached to the right wing of 26 adult quail while the left wing served as the intra-animal control. The stretch protocol was as follows: day 1 (10% wt), days 2 and 3 (rest), day 4 (15% wt), days 5–7 (rest), day 8 (20% wt), days 9 and 10 (rest), days 11–14 (25% wt), days 15 and 16 (rest), and days 17–38 (35% wt). Birds were killed after 12, 16, 20, 24, and 28 days of stretch not including rest days. Muscle mass increased 174% (12 days), 196% (16 days), 225% (20 days), 264% (24 days), and 318% (28 days). Muscle length increased 60% (12 days), 34% (16 days), 59% (20 days), 50% (24 days), and 51% (28 days). Mean fiber area increased 111% (12 days), 142% (16 days), 75% (20 days), 90% (24 days), and 39% (28 days). Fiber number, which was measured histologically, increased significantly by 82% only in the 28 days of stretch group. The percentage of slow tonic fibers did not change for any of the time points examined."[506.1]

Dosages

In terms of the supplements listed, I will give you the dosages I personally use, although your dosages truly depend on individual variables such as muscle mass, myogenic / lipolytic goals, and psychological thresholds. I will also tell you that I rarely combine all the supplements listed in each cycle due to the high accumulative cost, but I enjoy planning and formulating supplement protocols.

As for my favorite supplement brands:

- **Jarrow** for their Probiotic blends (Jarrow Dophilus, Fem-dophilus), Vitamins, Aminos, Herbal Extracts, and my favorite source of Quercetin.
- **NOW Foods** for their Protein Powders (10LB Whey Isolate Unflavored), *Essential oils*, Vitamins, Minerals, Aminos, Herbal Extracts, General Bulk Powders.
- **Nutricost** for Glycine and Serine Powder.
- **Swanson** for inexpensive plant extracts and probiotics (L. Rhamnosus, L. Plantarum).
- **Pure Encapsulations** for purified single component chemical supplements.
- **Naturemade** for Vitamins and Minerals.

GlySer: For Recreational Athletes: Chronic Mode (All Day): 0.2g x kg L-Glycine / 0.1g x kg L-Serine.
Acute Mode (Post-Exercise): 0.3g x kg L-Glycine / 0.1.5g x kg L-Serine.
For Professional Athletes: Chronic Mode (All Day): 0.3g x kg L-Glycine / 0.1.5g x kg L-Serine.
Acute Mode (Post-Exercise): 0.4g x kg L-Glycine / 0.2g x kg L-Serine.

Alpha-lipoic Acid: 500-600mg 2-3x/d with meals.
Ascorbic Acid: 2g (Tendon Injuries: 10g sipped all day).
Aspirin: 100-300mg 1x per day (Dosages > 600 strongly suppress COX-2).
B-Complex: 2-4caps/d (Morning).
Beta Alanine: 20-40g/d added to Myogenic Drink/Dessert.
Beta Carotene: 75,000iu/d (Morning or Evening).
Beta-Alanine + L-Histidine: 3/1 Ratio: Example: 30g BA / 10g LH.
Chelated Copper: 20mg/d (Morning or Evening).
Citric Acid: 2-6/d (Post-Workout).
Chromium Picolinate: 300mcg/d (Morning or Evening).
Creatine: 12g/d added to Myogenic Drink/or 2g added to each serving of Myogenic Dessert.
D3: 8,000iu/d (Morning or Evening).
DHA: 2-5g/d (Evening).
DHEA: 400mg/d (Split dosages, Morning & Evening).
EGCg: 2g/d (On empty Stomach in morning, 60-Minutes before food or other supplements).
EPA: 2-5g/d (Evening).
Eucalyptus Globulus oil: 1/10th teaspoon/d. (Not Recommended).
Free Base L-Carnitine: 10-30g/d (Post-Workout).
GABA: For (possible) B-Cell regeneration: 1g 3x/d, or 3g sipped in a drink all day. For GH Spikes: 2g added to Workout Shake (Consumed Pre/Post-Workout).
Gamma-Oryzanol: 2-4grams per day.
Iodine: 1mg/d (Morning).
L-Arginine: 20g (sipped only Intra-Workout, during workouts lasting longer than two hours to mitigate gastrointestinal distress).
L-Aspartate: 10-15g Pre-Workout.
L-Citrulline: 15-30g/d (Added to workout Protein Shake).
L-Glutamine: 15g added to workout Protein Shake, and 15-30g sipped all day if possible.
L-Ornithine: 5-10g/d (added to Whey Isolate or Water).
L-Theanine: 1:1 Ratio (1mg L-Theanine for every 2mg of Caffeine) added to Caffeinated Drink and 100mg acutely administered immediately before bed if caffeine is chronically consumed (400mg+ per day).
Lion's Mane Mushroom Powder: 1/2cup 1x or 2x/d (Post-Workout and / or Evening).
Lithium Carbonate (Prescription): 300mg/d.
Lithium Orotate: 30mg/d (Evening).
*Liquid or Encapsulated Melatonin: 0.500mg – 0.700mg x kg.
Lutein: 100-200mg/d (Morning or Evening).
MK7: 360mcg/d (Morning or Evening).
Milk Thistle Extract: 20-40 Capsules swallowed or blended into a shake, consumed twice a day.

MSM: 1g/d (Morning or Evening).
Nicotine: 0.32mg x kg (Average: Between 15-40mg, Primarily Intra/Post-Workout).
Potassium Chloride: 5g/d added to workout Protein Shake.
Quercetin: 2-3g once per day.
Salsalate: 1000mg 1-2x / day.
Selenium: 800mcg/d (Morning or Evening).
Sildenafil: 100-300mg/d ground with pill crusher added to workout Protein Shake.
Spirulina Platensis: 2tbsp/d (Post-Workout).
Vitamin E: 2,000mg/d (Morning or Evening).
Whey Isolate: 75-100g: 33% consumed 60-Minutes Pre-Workout; 33% consumed Immediately Pre-Workout, 33% consumed Immediately Post-Workout.
Zinc: 30mg/d (Morning or Evening).

*I often meet people who say Melatonin isn't effective, and that they've tried many different brands, and dosages, but I believe they do not quite comprehend its effectiveness because Melatonin's ability to promote "sleepiness" can be easily overcome through chronic caffeine or psychotropic medication use, if it is administered in too low of dosages, or if it administered only acutely. The best way to take Melatonin is through my Countdown Melatonin Administration Protocol, which mimics more accurately the body's natural secretion pattern of Melatonin from evening until bedtime. To follow this protocol, take 5-10mg *three hours* before going to bed, take another 5-10mg *two hours* before going to bed, take 5-10mg *one hour* before going to bed, and finally take 5-10mg *immediately* before going to bed.

It must also be mentioned that many commercial Melatonin supplements contain far less melatonin than advertised, and they may contain serotonergic contaminants that result in neurotoxicity upon digestion. If you therefore feel mentally strange or physiologically sickly after taking large dosages of Melatonin, you should try a more reputable brand, and test even higher dosages to confirm your suspicions of contamination.

Also, although the most scientific dosage recommended for Melatonin use is at or near 500 micrograms, which may be fine for a child, this is not suitable for an adult, as I and others who use Melatonin in an informed manner do not use it merely for the promotion of sleep, but also as a systemic-genetic antioxidant.

My Ideal Anti-Inflammation Supplementation, Exercise, & Modality Protocol (Updated)

Explanation: Most days I wake up and perform fasted cardio, not to stimulate autophagy, but to ensure the EGCg I take before this workout absorbs effectively. After my morning cardio is completed I prepare my Antioxidant Shake, and chug it rapidly, after which point I engage in a quick and efficient Warmup workout for the muscles I will train in the evening hours, after my Warmups I'll jump into my Ice Bath, which I have placed earlier in the day for convenience, to magnify the power of the antioxidants I take during these

hours. In the evening, I consume more protein powder and engage in my intense planned workout, after which point I take my evening supplements (probiotics and minerals), and have a sugary smoothie to promote probiotic survivability during digestion.

Note: I say *ideal* because as aforementioned I am currently unable to afford all of the supplements and healthfoods that the scientific minds (including myself) have elaborated on and detailed thus far in this book.

- **6:00AM EGCg FASTED ENDURANCE NEURAL ULTRAS:**

1. Immediately take EGCg, Alpha GPC, Sip Strong Cold Generic Green Tea during workout (Prepare Green Tea in Evening night before).
2. 60-Minutes ENU Cardio.
3. Make Antioxidant Shake:
   JUICE: Red Cabbage - Ginger Root - Tomatoes - Carrots - HG Barley Grass - Tuscan Kale - HG Rye Grass - Sauerkraut.
   POWDERS / RAW MATTER: Whey Isolate, Betaine, L-Ornithine, Chlorella, Rutin, PureHMO (Human Milk), Flower Petals, MSM, Mustard Powder, (Vegan Diet: Palmaria Palmata, Wakame).
   BLEND CAPSULES: Oleuropein, Quercetin, Milk Thistle Extract, Broccomax.
4. Chug Antioxidant Shake.
5. 30-Minute Ice Bath.

- **10:00AM VITAMINS (WITH BREAKFAST):** Vitamin K1, Vitamin K7, Vitamin A, Alpha Tocopherol, 300mg DHEA, Lactoferrin, Liquid D3, Jarrow B-Right, Lutein-Zeaxanthin,
- **10:00AM-4:00PM MYOGENIC DRINK:** Added to 64oz Stanley Bottle: Coconut Milk, Glycine, Serine, L-Theanine, Creatine, Agmatine, Beta-Alanine, Eucalyptus Globulus oil.
- **DIET:** 50% Coconut oil, 40% PJ Kabo's EVOO Extract, 10% Grapeseed oil added to each meal.

OPTION 1 (LIPOLYSIS): PAPRIKA CHICKEN: Ground Chicken, Paprika Powder, Vinegar, Soy-Free Mayo, Sea Salt.
OPTION 2 (MYOGENESIS): BEEF CHILI: Ground Beef, Onions, Tomato Sauce, Diced Tomatoes. Green Peppers, Fresh Mushrooms, Traditional Chili Seasoning, Organic Dark Red Kidney Beans.
OPTION 3 (MYOGENESIS): CHICKEN CHILI: Ground Chicken, Onions, Corn, Green Tomatoes, Tomato Sauce, Lime Juice, Fresh Mushrooms, Traditional Chili Seasoning, Organic Dark Red Kidney Beans.

- **MEAL SHAKES + MEAL SUPPS:** Whey Isolate, L-Histidine, Lion's Mane Powder, Hyaluronic Acid.
- CAPSULES: CLA, DHEA.
- **7:00PM SUPPLEMENTS + WORKOUT SHAKE (PRE/POST):** Super Omega EPA Caps, Melatonin, Zinc, Copper.

1. SHAKE: **POWDERS**: Whey Isolate, Spirulina, L-Glutamine, Taurine, L-Ornithine, L-Citrulline.
2. Chug Half of Workout Shake.
3. Engage in Designated Intense Evening Workout.

- **8:00PM POST-PM WORKOUT MYOGENIC MODALITIES:**

1. Chug Remainder of Workout Shake.
2. 30-Minutes Intense Sauna > 1h Arms / Legs Heat-pad Therapy.
3. Make Wild Blueberry Smoothie + Vanilla Coconut Milk + Glycine + Serine + L-Glutamine.
4. Take Encapsulated Probiotics: Femdophilus, L. Acidophilus, Jarrowdophilus Ultra, Jarrow L. Plantarum, Culturelle Extra Strength, Bacillus Coagulans, Lactobacillus Helveticus , Lactobacillis Rhamnosus.
5. Apply Sedating EO's to Pillow before bed: Lavender oil, Sandalwood oil.

Anti-Aging, Lifespan Extension, & Longevity Diets

Although moderate levels of cellular ROS enhance lifespan it is not as simple to suggest that promoting low grade inflammation will make us live longer, as there are many other factors in play regarding lifespan such as environmental toxins, including dietary toxins (heavy metals, plastics, Palmitic acid-rich processed foods, 21st Century VOC's) that bring us ever closer to the development of cancer, which is the primary cause of mortality in elderly individuals, with cardiovascular disease coming in second place.
Cancer may be combatted by using antioxidants, and cardiovascular disease may be combatted by engaging in different forms of cardiovascular exercise during a Pro-Inflammation Cycle, to promote systemic angiogenesis.

It is unfortunate that the dosages of phytochemicals and vitamins that our seniors use are so minute and inconsequential that they do not benefit from them—taking one multivitamin tablet or one fish oil capsule per day will not yield any results.

I used to consider caloric restriction to be a foolish diet to practice, as losing muscle mass will shorten one's lifespan, but now that I understand that the form of "caloric restriction" used in the newest scientific studies is merely carbohydrate restriction, I do

Regarding caloric restriction, it is quite clear that most weak and sickly elderly individuals suffer from hypoproteinemia, while still consuming large amounts of unhealthy carbohydrates and non-essential fats, which contributes to their premature deaths, alongside physical inactivity, prescription use, alcohol use, and NSAIDs. In these scenarios the macronutrient intake must be inverted, from low protein to high protein, from high carbohydrate to low carbohydrate, from low essential fat, to high essential fat. Furthermore, to ensure healthy aging it is essential to build as much muscle as possible through resistance training while also conditioning that muscle and by association the heart & brain with chronic cardiovascular exercise.

Suppressing mTOR and facilitating AMPK expression is another emerging science towards life extension, by caloric restriction (carbohydrate restriction), or the use of the AMPK agonist AICAR, or certain AKT pathway inhibiting phytochemicals (Silymarin: PTEN). Aging has been shown to cause noticeably reduced AMPK function and sensitivity:

"<>Recent studies have demonstrated a strong relationship between aging-associated reductions in mitochondrial function, dysregulated intracellular lipid metabolism, and insulin resistance. Given the important role of the AMP-activated protein kinase (AMPK) in the regulation of fat oxidation and mitochondrial biogenesis, we examined AMPK activity in young and old rats and found that acute stimulation of AMPK-alpha(2) activity by 5'-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR) and exercise was blunted in skeletal muscle of old rats. Furthermore, mitochondrial biogenesis in response to chronic activation of AMPK with beta-guanidinopropionic acid (beta-GPA) feeding was also diminished in old rats. These results suggest that aging-associated reductions in AMPK activity may be an important contributing factor in the reduced mitochondrial function and dysregulated intracellular lipid metabolism associated with aging."[506.1A]

Regarding longevity diets, including **Anti-diets** (a term I coin to refer to fasting protocols), that promote lifespan extension, here is a list of the five most common diets and anti-diets that extend lifespan.

Longevity Diets

1. Scientific Caloric Restriction (Moderate Protein-Moderate Fat-Low Carbohydrate): Increases lifespan through a suppression of the Akt pathway, and decreased mTOR expression.

2. Popularized / Antiquated Caloric Restriction (Starvation: Low Protein-Low Fat-Low Carbohydrate): Increases lifespan through a suppression of the Akt pathway, and a greater decrease in mTOR expression, but will result in frailty and is not recommended due to the risks of extended duration excessive autophagy.
3. The Ketogenic Diet (High Protein-High Fat-Zero Carbohydrate): Increases lifespan through a significant suppression of the Akt pathway but is higher in protein and therefore mTOR expression is still of concern, and we must remember that even dietary protein stimulates insulin release. Importantly, the Ketogenic Diet will increase muscle IL-6, which when combined with exercise will facilitate myogenesis and is likely to further enhance lifespan owing to the increased myogenic ability to recover from strenuous, leading to increased volitional exercise (longevity).

Anti-Diets

1. Intermittent Fasting / Time-restricted eating (24h): An Anti-Diet that increases lifespan through mTOR suppression, and decreased Akt pathway activity.
2. Prolonged fasting (72h+): An Anti-Diet that increases lifespan through significantly suppressed mTOR expression and Akt activity, and which although similarly inflammatory to the Ketogenic diet, is to be considered the hardest anti-diet to follow.

(Note on Anti-diets: These modes of eating will only increase lifespan when combined with a Ketogenic Diet or a Caloric Restriction diet. No amount of fasting will extend lifespan to a noticeable degree if during refeeding you eat improperly!)

It must be mentioned that lifespan will always be shortened by the restriction and deficiency of essential fatty acids, and essential nutrients, complicating estimations of diet-induced lifespan extension, and most importantly as a warning I must remind you, the reader, that *diets that restrict protein consumption will undoubtedly lead to accelerated aging in susceptible individuals*, indirectly, due to increased aging-related muscle loss, leading to decreased physical activity, meaning that protein consumption should be restricted only by individuals on anabolic steroids (+ high dose TRT), or who have accrued substantial muscle mass gains over their lifetime. Women should never restrict protein consumption nor engage in prolonged fasting after a certain age for the same reason.

Science may generally point to mTOR inhibition as being the key to lifespan extension, although it is not correct to suggest that restricting amino acids will always enhance lifespan, for we do not live in a controlled environment and are constantly assaulted with environmental toxins, natural, or unnatural, therefore severely complicating lifespan predictions. The loss of muscle mass that accompanies fasting may be relatively easy to

regain for a younger individual, and even older ones, if they are experienced at exercise and understand myogenesis sciences, but as aforementioned, when an elderly person experiences physical injury owing to frailty, the odds of them dying after hospitalization are extremely high. Thus, for those who do not excel at exercise, nor enjoy it, and have always had weak muscles, it is wiser to never restrict protein consumption, and only play with carbohydrate intake during caloric restriction, avoiding experimentation with prolonged fasting.

For a healthy adult man or woman, a life that revolves around chronic exercise and a low level of psychological stress, devoid of supplementation, will be sufficient to enhance lifespan to a significant degree by allowing Reactive Oxygen Species to do their evolutionary job, which is to promote both cognitive processes and mitochondrial efficiency. Conversely, for those who have experienced or are experiencing high levels of psychological stress or have been exposed to high concentrations of environmental toxins, and therefore have an acceleration of DNA damage, exercise may not be sufficient to counteract the genetic propensity to develop cancer, or neurodegenerative conditions, making antioxidants necessary to enhance lifespan and healthspan in those who have been scarred by the worlds hyper complex and deadly chemistry. One must remember that there is no panacea, one singular essential nutrient, phytochemical, or mycochemical will treat every health condition you have, and all antioxidants will fail in time if exercise is not performed, for physical exertion, most especially cardiovascular exercise, is the only physiological process capable of treating, but not curing, all ailments.

Although the Akt pathway has proven to play a pivotal role in diet-related aging through enhanced mTORC1 activity, carbohydrate consumption is necessary to feed beneficial intestinal microbiota, therefore in certain individuals a higher carbohydrate diet may extend their lifespan, if those carbohydrates come in the form of fermented foods, and low starch vegetables. I am of the opinion that if chronic cardiovascular exercise is engaged in (10+ Hours a week), and probiotics are supplemented, a diet high in healthy carbohydrates will not shorten lifespan. But for many, exercise is thought of as a chore, and therefore ignored, and in those cases carbohydrate restriction is clearly the most feasible option to enhance lifespan.

Regarding the hype around SIRT1, it is my opinion that upregulating PTEN expression, through inhibiting Protein Kinase B activity (i.e. the Akt Pathway: The Insulin pathway), and through its tumor suppressive effects, will be a much more efficacious way to extend lifespan [See: Anti-Inflammation Cycle Supplementation: Silymarin] than experimenting with supposed *Sirtuin Activity Boosters*.

IMC Blood Glucose Limits

Because blood glucose is measurable through over-the-counter glucometers, and blood sugar levels are intricately tied to not only obesity, but Insulin-induced aging, and because hyperglycemia damages blood vessels, which as we have learned thus far are essential components of muscle strength and neurological health, it is intelligent to test your postprandial (post meal) blood glucose around thirty minutes after eating, to figure out if your meal, which is hopefully a fixed meal (the same composition everyday), contains the correct portion of carbohydrates *and* protein, to monitor your average daily blood glucose levels. Interestingly, even amino acids such as Alanine, Glutamine, Aspartate, & Glutamate can cause a rise in blood glucose through Gluconeogenesis, a process in which amino acids are recycled to form glucose molecules, which is why it may be necessary to rebalance your meal plan, to restrict carbohydrates further. Your blood sugar level will give you a general idea if your insulin levels are high, and consequently if the Akt Pathway is overactive, balanced, or underactive, and if you are accelerating or delaying cellular aging.

Although many phytochemicals will lower blood glucose levels, it is wiser to focus on daily exercise involving glycogen exhaustion to maintain optimal blood glucose levels, such as cardiovascular exercise, versus high volume resistance training. Many individuals make the mistake of consuming an excess of daily carbohydrates while on exercise protocols involving higher load resistance training, assuming that their bodies will be able to utilize the dietary carbohydrates, but this is often not true, just because someone is not obese does not mean their blood glucose levels are well regulated. If you are using carbohydrates for the simple purpose of promoting exercise performance or fast twitch fiber growth and not for bulking (adipogenesis), I suggest that you consume smaller and more frequent meals of strictly planned out servings of carbohydrate-rich food, while also monitoring your blood glucose levels periodically to avoid promoting aging processes inadvertently.

If your blood glucose levels are consistently high, even when you are not consuming fast digesting carbohydrates or an excess amount of protein, and you are engaging in frequent exercise, it is possible that a drug you are using such as Caffeine or Nicotine is the cause of this derangement, by causing increased secretion of Cortisol, which promotes catabolic gluconeogenesis by sequestering amino acids from muscle tissue, or a supplement such as Creatine, which as we have learned is liable to cause Insulin Resistance through extended use, therefore you should decrease your use of the aforementioned drugs or supplements.

Regarding Hypoglycemia, it is not considered a beneficial biological state by most medical professionals, but it is important for activating the Counter-Regulatory Hormone

Response and it could possibly be a facilitator of angiogenesis. Exercise-induced drops in blood sugar are unavoidable on a diet, and should be sought after, since it is only when the blood sugar drops that the catabolic machinery of lipolysis initiates to the maximal degree. As for everyday life, and for the general population, severe hypoglycemia will not be of concern, considering most of the readers of this book are likely to live in a milieu of excess macronutrients, where snacks are commonplace, and refeeding opportunities are plentiful and convenient.

I categorize daily postprandial blood glucose levels into four **limit categories** or **stages** for health and longevity below:

Stage-1: 140mg/dL $^{+/- 5}$

Ideal for high carbohydrate diets, good health, moderate body fat.

Stage-2: 120mg/dL $^{+/- 5}$

Ideal for low carbohydrate diets, great health, moderate-low body fat.

Stage-3: 100mg/dL $^{+/- 5}$

Ideal for very low carbohydrate diets, increased longevity, low body fat.

Stage-4: 80mg/dL $^{+/- 5}$

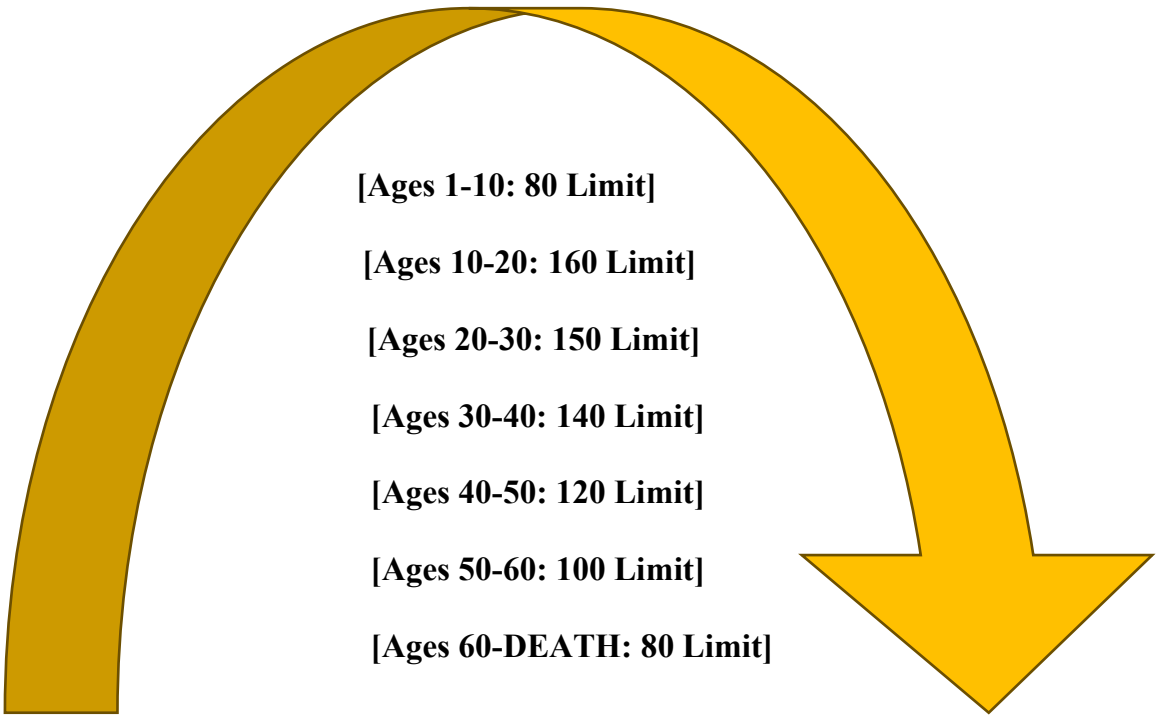
Ideal for Antidiets / Zero-K diets, maximized longevity, very low body fat.

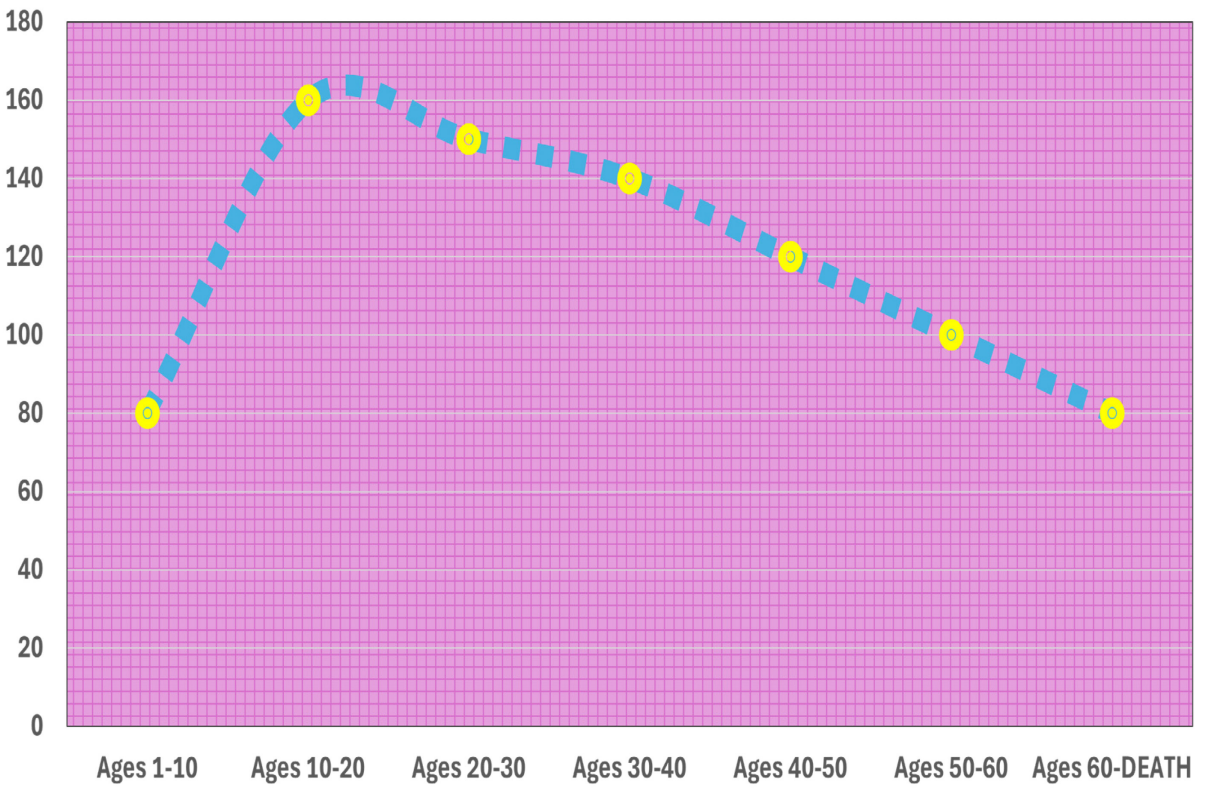
Note 1: If it is not clear to you, a strict diet must be followed to maintain not only blood glucose levels, but also to maximally stimulate anabolism. Those who treat food as a reward and not a fuel source are unintentionally aging themselves by the overconsumption of carbohydrates, fats, and even amino acids. The practice of dining out each week, or multiple times a week, at restaurants that serve unhealthy food, is most common in individuals that do not exercise intensely. They have not accelerated their metabolism through mechanotransduction, nor through ergogenic use, therefore the excess macronutrients they consume harm their bodies, not through the promotion of adipogenesis, but primarily through hyperglycemia and hyperlipidemia. Dining out on macronutrient dense food should be reserved for celebratory gatherings, or at the very least, if it is unavoidable for you and your family, intermittently as a way to reward yourself after engaging in the most strenuous exercise sessions that you have accomplished through following your chosen workout protocol. The best idea for a family who plans out once or twice monthly restaurant visits is it perform a group hike or bike ride for a very long duration (2-4 hours), to therefore prepare the body for the

upcoming macronutrient load. Those who are slave to sensory pleasures will expedite their aging-induced skeletal muscle and neurological dysfunction, be therefore wise not to unintentionally destroy your body in favor of bioengineered flavors.

Note 2: Please understand the following limits are only applicable for those who exercise daily, and they are useless if you do not follow a strictly planned, repetitive diet, that is unless you are constantly monitoring your postprandial blood glucose levels which will be quite tiresome for most people. If you do not exercise, your metabolism will be slowed, and any food that you do eat, including even seemingly safe fatty acids, will be far more likely to damage your body due to inefficient beta-oxidation and insidious lipid accumulation. Finally, these limits are potentially useless for Endurance Athletes who exercise in such what I would consider *the most ideal way* so as to render diet far less relevant to their health and longevity.

The IMC Optimal Diminishing Dietary Slope © (ODDS)


[Ages 1-10: 80 Limit]
[Ages 10-20: 160 Limit]
[Ages 20-30: 150 Limit]
[Ages 30-40: 140 Limit]
[Ages 40-50: 120 Limit]
[Ages 50-60: 100 Limit]
[Ages 60-DEATH: 80 Limit]



I have made the references on the previous page and line chart above to describe diminishing Blood Glucose Limits for what I consider to be an optimal guide for promoting healthspan. Healthspan is defined in my mind as being a balanced combination of brain-body wellness (stability), brain-body *adaptation, as well as a sufficient amount of longevity. A happy life is often more important to achieve than a *maximized efficiency life*. If you therefore enjoy consuming carbohydrates but also wish to extend your lifespan, please refer to the line chart on the following page.

Please remember that the Blood Glucose Limits of ages 10-30 are limits, they are not steady-state goal levels. If a teenager is to embrace this protocol and consume large amounts of slow digesting carbohydrates, or spike their blood sugar with real sugar soda during school hours, their blood glucose levels will still likely never go beyond 150. Because the median lifespan of an adult human (in the USA) is approximately seventy-five years of age, and cancer diagnosis generally coincides with this age range (65-70), the final stage of ODDS dieting will occur shortly before this period of time (Age 60). Once an older individual switches to the final 60-D ODDS stage, they have two options:

A. Restrict their carbohydrate intake to *only the lowest carbohydrate vegetables*, those with under 5-Grams per cup, such as cruciferous vegetables, green beans, okra, spinach, kale, lettuce, radishes, et cetera. Or if they engage in frequent exhausting cardiovascular exercise, owing to less stored glycogen and greater glucose disposal potential, they can consume small amounts of other carbohydrates, especially post-exercise.

B. Give up all carbohydrates for the rest of their life to maintain a long lasting neuroprotective and genoprotective ketogenic state, even at the cost of socio-sensory pleasures (this being essential to combat active or reoccurring aggressive cancers).

Important Reiteration: If you or a loved one is sickly, generally unhealthy, or taking a myriad of toxic pharmaceutical drugs, restricting blood glucose and thereby insulin levels may not benefit them as Insulin is not only anabolic, but also *antiapoptotic*. If a Ketogenic Diet is pursued, and protein intake is very high, this desired antiapoptotic effect will still be present due to mTOR and ketone production, but as we know, most elderly individuals do not eat very much, therefore if they are placed on a Ketogenic Diet, and do not consume large amounts of protein, or fat, they are likely to experience excessive autophagy, the sort common in Antiquated Caloric Restriction, which will only result in the exacerbation of their neurological and physical decline.

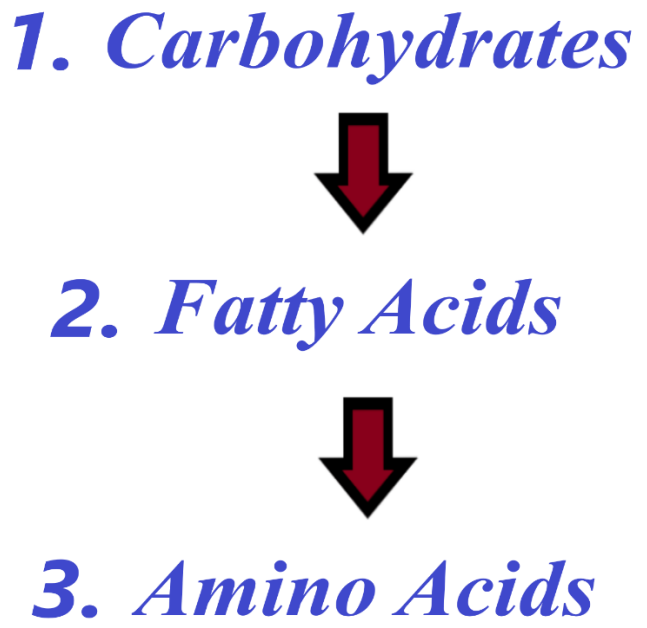
Also, ODDS is a protocol for those who consider diet to be a more valuable force of biological change than supplementation. Minimal supplementation will be required during ODDS, except for essential nutrients (vitamins, fatty acids, + coconut fatty acids). Combining antioxidants with a Ketogenic Diet is generally a bad idea, as interfering with IL-6 expression or Ketone production may drastically reduce the predicted lipolytic and longevity-induction effects associated with the Ketogenic Diet, but in old age (the final stages of ODDS), to avoid excessive IL-6 expression, Lactobacilli and Bifidobacterium Probiotic supplementation is suggested.

IMC ODDS is a biological protocol that is represented by the scalene triangle, which is asymmetrical in nature, just as human beings possess asymmetrical thought, and our environment is fraught with asymmetrical chaos.

*The difference between brain-body health and brain-body adaptation are often conflated by people who do not understand the dynamics of inflammation. Promoting and maintaining good health requires careful anti-inflammatory dieting, and pricey supplementation, whereas promoting the most natural forms of systemic adaptation requires negligible inflammatory dieting (not phytochemical rich), early life insulinemic intellectual work, and minimal supplementation.

A common trend in this book is that it is my recommendation that healthy brains and bodies should not restrict inflammation, especially when chronic exercise and intellectual work are pursued frequently, whereas unhealthy brains and bodies (not including obesity) require the restriction of inflammation alongside antioxidant-use to mitigate further cellular damage, and expedited death.

The Three Tier System of Dietary Restriction



I feel it necessary even if it is obvious to most to reinstate this vitally important point and force it into the psyche of uninformed individuals. Whether you are experimenting with Blood Glucose Limits, attempting to extend your lifespan, or burn fat, you should always adhere to what I refer to as the *Three Tier System of Dietary Restriction*: Carbohydrates should be restricted before fatty acids, and fatty acids should be restricted before amino acids, this will ensure that you do not lose an excessive amount of muscle tissue during subtle or severe dietary changes. Restricting protein intake for extended periods of time is the most advanced therapeutic and dangerous method to play with for lifespan extension, and when combined with physical inactivity, is clearly one of the leading causes of sarcopenia in the elderly. Generally speaking, if you wish to restrict your protein consumption to enhance lifespan, you should restrict all macronutrients, and simply go on a fast.

Insulin & AKT are bad… Right?

Actually, Insulin, and it's downstream protein, AKT, are excellent endogenously-produced nootropics by way of activating mTOR & ERK1/2 (enhanced Neurogenesis / Neuritogenesis), especially in younger brains. Healthy children should not have their dietary intake of slow digesting *carbohydrates restricted, and because eating has been and will always be a dietary social bonding experience, strange or extreme diets are liable to harm the interpersonal relationships of most individuals, therefore I have created what I refer to as a "Diminishing Dietary Slope", which describes the progressive and suggested age-related decreases in carbohydrate consumption based upon Blood Glucose Limits, which begins in early life with insulinemic Blood Glucose Limits to promote cognition and muscle growth, and invariably culminates in a zero-carbohydrate ketogenic diet to maintain targeted Blood Glucose Levels at the later stages of life to promote longevity.

Interestingly, you will notice the Blood Glucose Limit I have set is 80 for both the earliest and latest stages of life, this is because newborns and very young children's bodies do not produce large amounts of Insulin, because their pancreases are still developing, and parallel to this but explainable through different means, because the elderly do not require large amounts of Insulin or blood sugar due to having slower metabolisms and greater cellular senescence. After preteenhood (Age 9+) is reached the child's body begins to harness Insulin for its neurotrophic purposes, if you wish to learn more about the neurological benefits of Insulin please refer to the section Other Hormones (Non-Androgenic): Insulin: [C]. Although sweetened liquids are addictive, offering a teenager a real sugar soda to sip during their studies at school, or intra-exercise during high school sports is not a bad idea, if they are not obese, as this boost to insulin secretion will surely enhance their cognition.

Do not use traditional glucometers on your infant or child (that would be sadistic), I would instead wait until a smartwatch manufacturer acquires the rights to and begins incorporating laser-based blood glucose monitoring technology into their products. Also, understand that the following Blood Glucose Limits starting from Age 10 onward are for physically and mentally active human beings only, couch potatoes should always stay between Stages 3 / 2.

Regarding children, if a child shows signs of mental / neurological deterioration or any form of intellectual impairment it is a bad idea to feed them large amounts of carbohydrates, considering nearly every form of mental illness revolves around mitochondrial toxicity brought on by inflammation, the best treatment will be either a diet rich in phytochemicals combined with exercise, or a diet rich in lean meats with extremely low amounts of carbohydrates (modified ketogenic diets) combined with

exercise. Conversely, if you are raising a neurologically (psychologically) healthy preteen / teenager who engages in frequent intellectual work, and who has a forced or self-made exercise protocol, feeding them a diet of restricted carbohydrates will surely reduce their potential for maximizing their analytical and creative intelligence during their growth period. The aforementioned point also applies to you, the reader, if you are under the age of thirty, of normal body weight, and of sound mind.

*Because Fructose does not stimulate Insulin release, and yet still raises blood sugar, I do not suggest incorporating it into your ODDS diets, it will only be an unnecessary and complex variable to overcome, unless the consumed fructose comes paired with a dense concentration of polyphenols, such as with Wild Blueberries.

Telomeres, Sirtuins, & NAD+

Telomeres serve the purpose of protecting chromosomes. Chromosomes protect and compartmentalize DNA to allow it to fit into the nucleus of cells, thereby allowing DNA replication, which is a process necessary for cellular renewal. DNA replication is prone to errors which results in DNA damage, telomere shortening, and cellular senescence. Shortened Telomere length is not a direct cause of aging, but instead a sign of DNA damage, and therefore a relatively inaccurate estimation of lifespan.

"<>The last century has been characterized by an unprecedented rise in human life expectancy across the globe. This demographic trend, however, was generally not accompanied by the same extension in healthspan and productivity. This is because aging per se is the major risk factor for most pathological conditions that limit healthspan and promote chronic disorders affecting the elderly, including immuno-senescence, cardio-metabolic disorders, osteoporosis, sarcopenia, arthritis, cataracts, neurodegenerative diseases and most cancers.
<>Therefore, development of effective tools for slowing down the aging rate is currently a priority agenda for research organizations and for health policy makers across countries. In this context, an important task is the development of effective tools to evaluate the rate of aging both in individuals and in groups of patients participating in clinical trials specifically targeting aging and related multimorbidity. Historically, functional tests such as grip strength, walking speed, chair rising, and standing balance times were most commonly used in such studies. These tests, however, are too sensitive to transient changes in health status caused by non-chronic diseases such as colds and indigestion, so they can hardly provide a reliable estimate of the aging rate per se.
<>Therefore, considerable efforts were made over the past few decades to develop measures of biological aging which are reliable, precise, and robust. Among them, there

are parameters characterizing aging-related processes such as genomic instability, cellular senescence, DNA methylation, proteostasis, and mitochondrial function. None of the above measures, however, represent an exhaustive measure of biological age.
<>According to the American Federation for Aging Research (2016), a true biomarker of aging should meet the following criteria:

- Predict remaining life expectancy better than chronological age,
- Monitor mechanisms underlying the aging process but not a specific disease,
- Be subject to repeated tests without harming the individual,
- Be testable in both laboratory animals and humans.

<>Telomere length (TL) possesses many properties that make it suitable to be used as a biomarker of aging. Telomeres of vertebrates represent repetitive (TTAGGG)n sequences located at the ends of linear chromosomes. These chromosomal structures are known to be crucially involved in the process of cellular senescence and their age-associated shortening is commonly regarded as an important contributor to organismal aging. Therefore, TL is currently recognized by many authors as powerful biomarker of aging and aging-associated pathological conditions. The advantages of TL in order to be a biomarker of aging include a correlation with chronological age throughout the entire life course, predictive power for the disease condition and mortality and also large responsiveness to either adverse or beneficial exposures. <>Moreover, it is recognized as an attractive biomarker candidate to track changes in the human aging rate over the course of intervention trials designed to delay the onset or retard the progression of aging-associated pathological conditions. However, while TL satisfactorily meets the criteria 3 and 4 of the American Federation for Aging Research due to an opportunity to a minimally invasive, repeated testing without harm to human subjects and a testability in both laboratory animals and humans, its compliance with the criteria 1 and 2 is rather questionable.
<>Presently, peripheral blood leukocyte TL (LTL) is often identified in cross-sectional and longitudinal analyses when certain patient cohorts are compared to age- and sex-matched individuals. However, even though convincing evidence has been obtained from in vitro and in vivo models that TL reflects levels of both the cellular senescence and chronic disease-related oxidative stress, epidemiological and clinical findings are far less conclusive. Indeed, a large inconsistency was observed among studies. Such a discrepancy could be, at least partly, attributable to differences in the methods of TL measurement and statistical modeling used, variations among investigated populations, etc. This inconsistency was, however, so great that some authors have even questioned whether the link between TL and aging-associated processes really exists and,

consequently, it has led to hot debates about whether TL is really a reliable and valid tool to evaluate the rate of aging in human populations. <>Moreover, the phenomenon of the age-related telomere shortening is extremely complex and biological mechanisms underlying this process are not yet definitively established. In particular, it remains still unclear whether telomeric aging reflects a mitotic clock-like process or it is rather a biomarker of stress or a biological mechanism that transfers stress-associated signals to the cell. If the latter, telomere shortening can be rather a proxy for life-course stress exposures than a genuine cause of aging. Nevertheless, despite this uncertainty, TL currently remains one of the most widely used biomarkers of aging in epidemiological and clinical studies. In recent years, TL is also being increasingly used as a potential biomarker in personalized medicine."[506.2]

[B] Sirtuins, especially Sirtuin 1 (SIRT1), are enzymes that promote lifespan primarily through increased autophagy, through upregulation of AMPK and PGC1a[1], followed by anti-inflammatory effects. SIRT1 also plays a role in neurological aging and may protect the brain from dementia[2]. Sirtuins require NAD+ as a cofactor to function.

[1] "<>Autophagy refers to the lysosomal degradation and recycling of intracellular components such as proteins and organelles, as well as foreign pathogens that enter the cytoplasm. During the aging process, autophagy dysfunction results in the loss of proteostasis that characterizes all old organisms. SIRT1 activates autophagy in cancer cells through deacetylation of the autophagy-related proteins LC3 and unc-51 like kinase 1 (ULK1). The activation of SIRT1 in motoneurons stimulates autophagy and motor nerve regeneration after injury through HIF-1α. In a mouse model of nonalcoholic fatty liver disease (NAFLD), SIRT1 promotes lipid autophagy through the peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) pathway.
<>Additionally, SIRT1 can activate autophagy through AMP-activated protein kinase (AMPK). For instance, hepatic SIRT1 overexpression in glucose-6-phosphatase-α-deficient mice corrects impaired AMPK signaling, restores defective autophagy, and rectifies metabolic abnormalities. MiRNAs can regulate autophagy through targeting SIRT1. For instance, miR-124 and miR-142 represses autophagy in lung cancer cells by directly downregulating SIRT1. Silencing of miR-150-5p increases autophagy and ameliorates diabetic nephropathy in mice by activating SIRT1 and AMPK. In a mouse model of lung ischemia/reperfusion injury of the lung, miR-145 inhibition upregulates SIRT1 and attenuates cytotoxic autophagy via nuclear factor kappa-B (NF-κB)-dependent mechanisms.
<>SIRT6 overexpression increases autophagy and relieves lipopolysaccharide (LPS)-induced acute kidney injury in mice. SIRT6 induces autophagy in human bronchial

epithelial cells through attenuation of the insulin-like growth factor (IGF) signaling pathway. SIRT6 overexpression in lipid-laden macrophages upregulates the autophagy effectors ATG5, LC3B and LAMP1, induces autophagy, and increases cholesterol efflux, suggesting that SIRT6 helps protect against the development of atherosclerosis, an aging-related disease. SIRT6 also promotes autophagy in cardiomyocytes and protects against isoproterenol-induced cardiac hypertrophy through inhibition of the Akt signaling. By upregulating autophagy, SIRT1 and SIRT6 may slow down the aging process and increase life expectancy."

"<>SIRT1−/− mice under particulate matter exposure exhibit increased NFκB activation and aggravated lung inflammation. In keeping with this, SIRT1 overexpression downregulates NFκB and curbs the aggressiveness and inflammatory response of fibroblast-like synoviocytes in rheumatoid arthritis. As such, SIRT1 has emerged as a valuable therapeutic target for aging-related diseases associated with inflammation.

<>SIRT6 also regulates inflammatory responses. In a mouse model of cutaneous wounds, pharmacological activation of SIRT6 reduces tumor necrosis factor-alpha (TNF-α) secretion and accelerates the healing process."

"<>Mechanistically, SIRT1 and the histone acetyltransferase p300 form a fasting-inducible switch that maintains hepatic glucose production through sequential induction of CREB-regulated transcription coactivator 2 (CRTC2) and PGC-1a/FOXO1. SIRT1 also participates in the regulation of glucose and lipid metabolism by activating AMPK, a master regulator of energy homeostasis SIRT1 upregulation in diabetic mice lowers serum glucose levels and reduces fat mass accumulation through the activation of PGC-1α and AMPK."

↓ continued

[2] "<>Aging is the central risk factor for neurodegeneration. Owing to the lack of effective treatment options, neurodegenerative diseases are a large and increasing health burden worldwide. Alzheimer's disease (AD) is the most common form of age-related irreversible dementia that is characterized with progressive memory deficit and severe cognitive decline. It is a disorder that comes with complex biological dysfunctions such as chronic inflammation, DNA damage, and homeostasis instability. SIRTs have been considered a promising avenue in therapeutic intervention of neurological diseases such as AD.

<>During normal aging, SIRT1 is responsible for the maintenance of neural systems and behavior, including the modulation of synaptic plasticity and memory processes. The accumulation of amyloid-β (Aβ) plaques and tau-protein "tangles" in the brain is a pathological hallmark of AD. SIRT1 overexpression reduces Aβ-induced lesions in human microglial cells. SIRT1 also regulates the O-GlcNAcylation and phosphorylation of tau, suggesting that SIRT1 may influence tau deposition during the development of

AD. In addition, SIRT1 may attenuate the accumulation of Aβ and tau through the inhibition of neuroinflammation."[506.2.1]

[C] NAD+ (Nicotinamide Adenine Dinucleotide) is a coenzyme that is an essential component of redox reactions, where it takes electrons from substrates such glucose and fatty acids, becoming NADH, and facilitating ATP production. NAD+ associates with DNA repair and is necessary for sirtuin production. Nicotinamide (NAM) is a derivative of Niacin and converts to NAD+ in the body.

"<>Cellular NAD+ level and, thereby, the NAD+/NADH ratio affect not only ATP synthesis, but also generation of reactive oxygen species (ROS). Therefore, NAD+ is believed to be involved in aging as well as many pathological conditions. NAM-mediated increase in NAD+ level lead to reduced ROS generation from mitochondria through multiple mechanisms (summarized in Figure 1).
<>First, elevation in NAD+/NADH leads to reduced mitochondrial membrane potential, decreasing the chance for superoxide generation through retro-transport of electrons. Second, high NAD+ level facilitates activation of proteins involved in mitochondria quality control, such as SIRT1 and SIRT3, NAD+-dependent deacetylases functioning in metabolic homeostasis, cell survival and proliferation, stress resistance, and mitochondria maintenance.
<>SIRT1 activity facilitates mitochondrial maintenance by promoting their turnover through mobilization of factors involved in mitochondria biogenesis (peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1)α) and mitophagy (autophagy gene proteins, ATGs). It also facilitates cellular anti-oxidative defense through activation of forkhead box protein O (FoxO) proteins, which induce manganese-dependent superoxide dismutase (MnSOD) and catalase. Meanwhile, SIRT3 activity suppresses mitochondrial ROS generation through activation of MnSOD. It also promotes mitochondrial integrity by inducing closure of the mitochondrial permeability transition pore (mPTP) through deacetylation of mitochondrial matrix protein cyclophilin D. These anti-oxidative and pro-mitochondrial effects of SIRT1 and SIRT3 proteins function critically in protection of neurons and other cells that are otherwise vulnerable to oxidative stress and in extension of in vitro replicative life spans of human cells, including bone marrow stem cells.
<>Third, NAM's anti-oxidative effects may also be driven by direct inhibition of poly (ADP-ribose) polymerases (PARPs). PARPs protect genome integrity by binding to DNA at the sites of strand breaks and recruiting DNA repair enzymes. In doing so, they degrade NAD+ and generate NAM and ADP-ribose. Activated PARPs induce inflammation through activation of nuclear factor-κB (NF-κB). By acting as a feedback

inhibitor to PARPs, NAM attenuates inflammation and thereby exerts anti-oxidative and therapeutic effects against inflammation-associated diseases."[506.2.2]

[C2] Interestingly, because NAD+ is a byproduct of Niacin metabolism, and Niacin has been shown to substantially enhance NAD+ levels, this renders overpriced Nicotinamide & NAD+ boosters *unnecessary*.

"<>NAD+ is a redox-active metabolite, the depletion of which has been proposed to promote aging and degenerative diseases in rodents. However, whether NAD+ depletion occurs in patients with degenerative disorders and whether NAD+ repletion improves their symptoms has remained open.
<>Here, we report systemic NAD+ deficiency in adult-onset mitochondrial myopathy patients. We administered an increasing dose of NAD+-booster niacin, a vitamin B3 form (to 750-1,000 mg/day) for patients and their matched controls for 10 or 4 months, respectively. Blood NAD+ increased in all subjects, up to 8-fold, and muscle NAD+ of patients reached the level of their controls. Some patients showed anemia tendency, while muscle strength and mitochondrial biogenesis increased in all subjects. In patients, muscle metabolome shifted toward controls and liver fat decreased even 50%.
<>Our evidence indicates that blood analysis is useful in identifying NAD+ deficiency and points niacin to be an efficient NAD+ booster for treating mitochondrial myopathy."[506.2.3]

[D] Certain amino acids associate with muscle loss in the elderly. The elderly should avoid L-Glutamine and L-Proline supplementation in favor of chronic L-Histidine & Tryptophan supplementation alongside antioxidant use.

"<>Background and purpose: Metabolome analyses have shown that plasma amino acid profiles reflect various pathological conditions, such as cancer and diabetes mellitus. It remains unclear, however, whether plasma amino acid profiles change in patients with sarcopenia. This study therefore aimed to investigate whether sarcopenia-specific changes occur in plasma amino acid profiles.
<>Methods: A total of 153 community-dwelling and seven institutionalized elderly individuals (56 men, 104 women; mean age, 77.7±7.0 years) were recruited for this cross-sectional analysis. We performed a comprehensive geriatric assessment, which included an evaluation of hand grip strength, gait speed, muscle mass and blood chemistry, including the concentration of 18 amino acids.
<>Results: Twenty-eight of the 160 participants met the criteria for sarcopenia established by the Asian Working Group on Sarcopenia in Older People. Univariate

analysis revealed associations between the presence of sarcopenia and a higher plasma concentration of proline and glutamine, lower concentrations of histidine and tryptophan. Multivariable analysis revealed that a higher concentration of proline was the only variable independently associated with sarcopenia."[506.3]

[E] PTEN promotes lifespan through multiple mechanisms, the primary one being accelerating metabolism by enhancing the activity of brown fat, the second is the destruction of cancer cells.
[See: Anti-Inflammation Cycle Supplementation: Silymarin]

"<>To address the impact of Pten on health span and longevity, we followed cohorts of Ptentg mice, together with their WT littermates, during their entire life span. Importantly, both male and female Ptentg mice showed a significant increase in longevity as indicated by their Kaplan-Meier survival curves, median survival, and maximal life span. In particular, the mean longevity of the oldest 20% mice was significantly increased both in males (+16%) and in females (+9%) (p values of 0.003 and 0.009, respectively), and the mean longevity of the oldest 10% of mice was also significantly increased in both sexes. <>Additional statistical tests (Cox regression) indicated that the increased survival of Ptentg mice was dependent on the transgene and independent of other variables, such as the identity of the parents or the date of birth. We also wondered whether the effect of the transgene in longevity was a consequence of its protective effect on cancer. However, cancer-free Ptentg mice also showed an increased longevity when compared with cancer-free WT mice. This indicates that Ptentg extends longevity independently of its effect on cancer protection and suggests a direct impact on health span.
<>Given the lack of precedents linking Pten to energy expenditure, we have characterized this phenotype in further depth. Using rigorous calorimetric tests, we demonstrate that transgenic Pten mice have an increased energy expenditure, which is associated with lower adiposity and lower body weight despite being hyperphagic. Energy expenditure is a leading concept in metabolism that is emerging as a relevant determinant of longevity. Notably, a positive association has been reported between the individual values of energy expenditure of young mice and their subsequent life span.
<>The impact of energy expenditure on physiology and longevity is multifaceted. Energy expenditure associated to mitochondrial uncoupling protects cells from mitochondrial damage according to the so-called "uncoupling to survive" hypothesis. Even if restricted to a specific tissue, increased energy expenditure has important systemic beneficial effects by consumption of nutrients, which are thereby diverted from storage and its associated systemic damage. For example, relevant for our work, localized overexpression of Ucp1 in muscle improves insulin sensitivity, protects mice under HFD

from obesity and insulin resistance, and increases longevity. Also, lifelong treatment of mice with a mitochondrial uncoupler increases energy expenditure and extends longevity. Consistent with their increased energy expenditure, Ptentg mice present a number of systemic beneficial effects on health, including improved insulin sensitivity, protection from HFD-induced diabetes and steatosis, and protection from DNA damage associated to aging in the liver, which together are likely to contribute to the extended longevity of these mice.
<>We show with a variety of assays, including histology, functional glucose uptake, and gene expression, that the BAT of Ptentg mice is hyperactive. This has been confirmed in in vitro assays using isolated brown adipocytes, thus indicating that the effects of Pten on brown adipocytes are, at least in part, cell autonomous."[506.4]

[E2] PTEN reduces neurite outgrowth because it is an Akt Pathway inhibitor, which means it reduces Protein Kinase B (AKT). I do not consider this a deleterious effect considering that the only *healthy* individuals who will benefit from increased PTEN activity are those who are middle-age and elderly, because AKT, although important for brain development and synaptic plasticity in early life, loses some its benefits later in life. Furthermore, the goal of any middle-aged / elderly person should be to maintain brain functionality, not to grow brain cells, because growth factors fuel the proliferation of cancer cells. It is the natural order to learn the most amount of information and be inflamed in early life, and to quell inflammation and reflect on learned information (wisdom) in later life.

"<>The mechanisms of neuronal differentiation in PC12 cells are still not completely understood. Here, we report that the tumor suppressor PTEN has a profound effect on differentiation by affecting several pathways involved in nerve growth factor (NGF) signaling. When overexpressed in PC12 cells, PTEN (phosphatase and tensin homologue deleted on chromosome ten) blocked neurite outgrowth induced by NGF. <>In addition, these cells failed to demonstrate the transient mitogenic response to NGF, as well as subsequent growth arrest. Consistent with these observations was a finding that PTEN significantly inhibits NGF-mediated activation of the members of mitogen-activated protein kinase kinase (MEK)/mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/AKT signaling pathways, crucial for these processes."[506.4.1]

[F] Serine, Threonine, & Valine are the primary pro-aging amino acids through enhancing mTOR and sphingolipid production. Serine is still to be considered an essential amino acid for both athletes & the elderly, but if one does not engage in

frequent, exhausting exercise, there is no reason to consume an excessive amount of GlySer.

"<>Our genetic and biochemical analysis revealed that the yeast amino acid response relies on at least two different pathways: the well-characterized TORC1-S6K pathway, which has been described as an integrator of different nutrient and energy signals in organisms including humans and the sphingolipid-dependent Pkh1/2 pathway, also shown to promote aging in yeast.
<>Threonine and valine activated the TORC1 pathway and promoted cellular sensitization that could be reversed by the well-established anti-aging drug rapamycin, whereas serine specifically activated Pkhs and promoted cellular sensitization by a mechanism, which could be reversed by the Pkh inhibitor myriocin. <>Considering that L-serine is the substrate of the serine palmitoyltransferase, the α-oxamine synthase enzyme that catalyzes the condensation reaction of L-serine and palmitoyl-CoA to form 3-ketodihydrosphingosine, we propose that serine may activate Pkh by enhancing the first and rate-determining step of the sphingolipid biosynthesis pathway. Thus, serine administration may be equivalent to enhance sphingolipid biosynthesis, which is known to activate Pkhs and promote aging. This hypothesis is supported by the overlap between the treatment with the sphingolipid biosynthesis inhibitor myriocin and Pkhs impairment.[506.4A]

[G] Decanoic Acid i.e. the MCT oil fatty acid Capric Acid suppresses mTORC1 expression, making it an antiaging compound.

"<>Low-glucose and -insulin conditions, associated with ketogenic diets, can reduce the activity of the mechanistic target of rapamycin complex 1 (mTORC1) signaling pathway, potentially leading to a range of positive medical and health-related effects. Here, we determined whether mTORC1 signaling is also a target for decanoic acid, a key component of the medium-chain triglyceride (MCT) ketogenic diet.
<>Using a tractable model system, Dictyostelium, we show that decanoic acid can decrease mTORC1 activity, under conditions of constant glucose and in the absence of insulin, measured by phosphorylation of eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1). We determine that this effect of decanoic acid is dependent on a ubiquitin regulatory X domain-containing protein, mediating inhibition of a conserved Dictyostelium AAA ATPase, p97, a homolog of the human transitional endoplasmic reticulum ATPase (VCP/p97) protein.
<>We then demonstrate that decanoic acid decreases mTORC1 activity in the absence of insulin and under high-glucose conditions in ex vivo rat hippocampus and in tuberous

sclerosis complex (TSC) patient-derived astrocytes. Our data therefore indicate that dietary decanoic acid may provide a new therapeutic approach to down-regulate mTORC1 signaling."
"<>Inhibition of mTORC1 has been suggested to provide wide-ranging clinical benefits, including as a treatment for cancer, epilepsy, neurodegenerative diseases, and aging. The recent development of new pharmacological inhibitors for mTORC1 inhibition, based around rapamycin, have focused on identifying "rapalogues" without the toxicity associated with rapamycin.
<>Alternately, inhibition of this pathway is possible through dietary treatment, namely the classical ketogenic diet; however, this diet is highly restrictive for patients, resulting in low compliance. Our data suggest that a nonketogenic decanoic acid-rich diet that is less restrictive and avoids the potential adverse effects of ketosis could also provide therapeutic effects through inhibiting this pathway. Thus, further investigation into dietary decanoic acid may provide a useful approach to treat mTORopathies in addition to providing a range of associated health effects.[506.4A2]

[H] Leucine stimulates Sirtuin-1 expression in skeletal muscle, leading to mitochondrial biogenesis, which leads me the conclusion that *amino acid deprivation with Leucine supplementation* may exert antiaging effects in at the very least our skeletal muscle cells.

"<>Background: The effects of dairy on energy metabolism appear to be mediated, in part, by leucine and calcium which regulate both adipocyte and skeletal muscle energy metabolism. We recently demonstrated that leucine and calcitriol regulate fatty acid oxidation in skeletal muscle cells in vitro, with leucine promoting and calcitriol suppressing fatty acid oxidation. Moreover, leucine coordinately regulated adipocyte lipid metabolism to promote flux of lipid to skeletal muscle and regulate metabolic flexibility. We have now investigated the role of mitochondrial biogenesis in mediating these effects.
<>Methods: We tested the effect of leucine, calcitriol and calcium in regulation of mitochondrial mass using a fluorescence method and tested mitochondrial biogenesis regulatory genes as well mitochondrial component genes using real-time PCR. We also evaluated the effect of leucine on oxygen consumption with a modified perfusion system.
<>Results: Leucine (0.5 mM) increased mitochondrial mass by 30% and 53% in C2C12 myocytes and 3T3-L1 adipocytes, respectively, while calcitriol (10 nM) decreased mitochondrial abundance by 37% and 27% ($p < 0.02$). Leucine also stimulated mitochondrial biogenesis genes SIRT-1, PGC-1alpha and NRF-1 as well as mitochondrial component genes UCP3, COX, and NADH expression by 3-5 fold in C2C12 cells ($p < 0.003$). Adipocyte-conditioned medium reduced mitochondrial

abundance ($p < 0.001$) and decreased UCP3 but increased PGC-1alpha expression in myocytes, suggesting a feedback stimulation of mitochondrial biogenesis. Similar data were observed in C2C12 myocytes co-cultured with adipocytes, with co-culture markedly suppressing mitochondrial abundance ($p < 0.02$). Leucine stimulated oxygen consumption in both C2C12 cells and adipocytes compared with either control or valine-treated cells. Transfection of C2C12 myocytes with SIRT-1 siRNA resulted in parallel suppression of SIRT-1 expression and leucine-induced stimulation of PGC-1alpha and NRF-1, indicating that SIRT-1 mediates leucine induced mitochondrial biogenesis in muscle cells."[506.4A3]

Anti-Aging Subsection: Acrolein

[A] Acrolein, an environmental toxin found in ambient air, foods, and drinks, contributes to accelerated aging through DNA damage. Acrolein forms most especially in heated cooking oils high in Linoleic & Linolenic acid, thereby explaining the often misguided but somewhat valid medical attacks on fried foods. Acrolein is clearly a neurotoxin, but more relevantly, it accumulates in skeletal muscle, resulting in myogenic toxicity. Cooking food with vegetable oils heated to temperatures at or below 200 Degrees Fahrenheit or 93 Degrees Celsius should not result in a large formation of Acrolein, as Fried Food is the primary source of Acrolein consumption.

"<>Acrolein is a structurally simple α,β-unsaturated aldehyde present in the environment, water and food due to all kinds of human activities, such as high-temperature cooking, fossil fuel combustion, vehicle exhaust emission and insecticide abuse. Human exposure to acrolein primarily occurs through air inhalation, dietary intake and endogenous release. Exogenous or endogenous acrolein can exert deleterious health effects due to its high toxicity. Given its highly electrophilic structure, acrolein can easily bind to some nucleophilic biomacromolecules, such as protein and nucleic acids. The binding of acrolein to biomacromolecules results in oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction or even inflammation and abnormal immune responses. <>Over the past few decades, numerous studies have investigated the relationship between acrolein and diseases, especially several chronic diseases, including cardiovascular disease, alcoholic liver disease, Alzheimer's disease, diabetes and chronic obstructive pulmonary disease (COPD). Furthermore, recent studies have found that acrolein-induced DNA damage contributes to tumourigenesis. As a result of the ubiquitous sources and potential health risks of acrolein, the U.S. Environmental Protection Agency has listed acrolein as a high-priority toxic chemical."

“<>In 2013, Endo et al. suggested that linolenic acid may be the main source of acrolein from heated vegetable oils and described the mechanism of its generation. Specific hydroperoxide and epidioxide are the key intermediates in acrolein formation. By following the idea of Esterbauer’s review, Ewert elucidated a similar mechanism of acrolein formation from linoleic acid. In a recent study, Kato et al. also confirmed that the singlet oxygen oxidation products of linoleic acid and linolenic acid, but not oleic acid, are significant sources of acrolein formation. <>Moreover, acrolein was confirmed to be the major volatile in the early stages of fish oil oxidation and may be responsible for flavour deterioration. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), the common ω-3 fatty acids in fish oil, can also be the precursors of acrolein and Shibata inferred their related decomposition mechanism.”[506.4B]

[A2] Acrolein causes muscle atrophy.

“<>The toxic aldehydes acetaldehyde and acrolein were previously suggested to damage skeletal muscle. Several conditions in which exposure to acetaldehyde and acrolein is increased were associated with muscle wasting and dysfunction. These include alcoholic myopathy, renal failure, oxidative stress, and inflammation. A main exogenous source of both acetaldehyde and acrolein is cigarette smoking, which was previously associated with increased muscle catabolism. Recently, we have shown that exposure of skeletal myotubes to cigarette smoke stimulated muscle catabolism via increased oxidative stress, activation of p38 MAPK, and upregulation of muscle-specific E3 ubiquitin ligases.
<>In this study, we aimed to investigate the effects of acetaldehyde and acrolein on catabolism of skeletal muscle. Skeletal myotubes differentiated from the C2 myoblast cell line were exposed to acetaldehyde or acrolein and their effects on signaling pathways related to muscle catabolism were studied.
<>Exposure of myotubes to acetaldehyde did not promote muscle catabolism. However, exposure to acrolein caused increased generation of free radicals, activation of p38 MAPK, upregulation of the muscle-specific E3 ligases atrogin-1 and MuRF1, degradation of myosin heavy chain, and atrophy of myotubes. Inhibition of p38 MAPK by SB203580 abolished acrolein-induced muscle catabolism.
<>Our findings demonstrate that acrolein but not acetaldehyde activates a signaling cascade resulting in muscle catabolism in skeletal myotubes. Although within the limitations of an in vitro study, these findings indicate that acrolein may promote muscle wasting in conditions of increased exposure to this aldehyde.”[506.4C]

[B] Carnosine, even having low bioavailability, has been shown to bind to Acrolein and result in its excretion, making it an antiaging substance.

"<>Interestingly, our findings also suggest that carnosine supplementation is able to significantly reduce the percentage of excreted adducts in reduced form (54.70% ± 6.9 for control, 51.18 ± 8.4% for placebo and 43.78 ± 5.5% for carnosine). However, further investigations are needed to clarify the mechanism leading to such a change, although a possible explanation is that the increase of adducts concentration challenges the metabolic systems responsible for adduct reduction.
<>Although carnosine experimentation in humans have been limited so far by its low bioavailability, the findings herein reported demonstrate that carnosine is able to trap acrolein in vivo despite undetectable plasma concentration. Moreover, the adducts herein described are consistent with the RCS trapping mechanism previously described in vitro and in animal models that demonstrated the efficacy of carnosine and some analogues with improved activity and better metabolic stability"[506.4D]

[B2] Beta-Alanine (Carnosine) decreases Acrolein concentrations in *exercised* skeletal muscle. This is a very interesting study that equates to Beta-Alanine becoming a future myogenic longevity supplement.
"<>Previous studies have demonstrated that exercise results in reactive aldehyde production and that β-alanine supplementation increases carnosine content in skeletal muscle. However, little is known about the influence exercise and β-alanine supplementation have on the formation of carnosine-aldehydes. The goal of the present study was to monitor the formation of carnosine-aldehyde adducts, following high-intensity intermittent exercise, before and after β-alanine supplementation. Vastus lateralis biopsy samples were taken from 14 cyclists, before and after a 28 day β-alanine supplementation, following 4 bouts of a 30 s all-out cycling test, and carnosine and CAR-aldehyde adducts [carnosine-acrolein, CAR-ACR (m/z 303), carnosine-4-hydroxy-2-hexenal, CAR-HHE (m/z 341) and carnosine-4-hydroxy-2-nonenal, CAR-HNE (m/z 383)] were quantified by HPLC-MS/MS.
<>β-alanine supplementation increased muscle carnosine content by ~50% ($p = 0.0001$ vs. Pre-Supplementation). Interestingly, there was a significant increase in post-exercise CAR-ACR content following β-alanine supplementation ($p < 0.001$ vs. post-exercise before supplementation), whereas neither exercise alone nor supplementation alone increased CAR-ACR formation.
<>These results suggest that carnosine functions as an acrolein-scavenger in skeletal muscle. Such a role would be relevant to the detoxification of this aldehyde formed during exercise, and appears to be enhanced by β-alanine supplementation. These novel findings not only have the potential of directly benefiting athletes who engage in intensive training regimens, but will also allow researchers to explore the role of muscle

carnosine in detoxifying reactive aldehydes in diseases characterized by abnormal oxidative stress."[506.4E]

[C] Acrolein forms through high heat exposure most especially in vegetable oils that experience photo-irradiation, making it necessary to only purchase vegetable oils in amber bottles, and store them in dark areas.

"<>The above results strongly suggested that the presence of 1O2 oxidation-specific HpODE (i.e., 10- and 12-HpODE) and HpOTE (i.e., 10- and 15-HpOTE) isomers increase the amount of acrolein formed. Considering our previous report demonstrating that the irradiation of edible oils with daily levels of light induce 1O2 oxidation18, the use of such edible oils oxidized by 1O2 oxidation would increase the exposure and dietary intake of acrolein.
<>Therefore, we then investigated whether photo irradiation increases the amount of acrolein generated from edible oils. Since this study newly suggested that LA is a potential source of acrolein, edible oils that possess different compositions of LA were used: rapeseed oil (OA: 65.2%, LA: 19.5%, LnA: 7.7%), rice bran oil (OA: 44.9%, LA: 34.7%, LnA: 1.0%), and soybean oil (OA: 23.2%, LA: 54.9%, LnA: 6.6%)10. Edible oils were each oxidized by pre-irradiation under 5000 lux (16–18 °C) for 0–7 days assuming the storage of edible oils on shelves on the market or at homes. Subsequently, the oxidized oils were heated at 180 °C for 90 seconds.
<>Edible oils placed in the dark did not produce acrolein by the heating process (Fig. 6). On the other hand, as we expected, the amount of acrolein generated from photo-irradiated edible oils increased with pre-irradiation time."
"<>Storage and culinary processes during the daily use of edible oils expose them to light. Therefore, antioxidative measures to prevent photo oxidation (1O2 oxidation), for example, the addition of 1O2 trapping reagents (e.g., carotenoids) and improvement of packaging techniques (e.g., use of amber bottles), may contribute to the reduction of acrolein formed from edible oils and to dietary exposure."[506.4F]

[See: Mitochondria]

[See: AGE Inhibitors: Alpha-lipoic acid]

[See: Fasting]

[See: Anti-Inflammation Cycle Supplementation: Silymarin]

The Skin

The primary cause of superficial aging is by way of solar radiation, this is called Photoaging. Many essential oil chemical components will either halt photoaging, or possibly reverse it through decreasing inflammation and / or promoting collagen synthesis, but there are two other options. I'd like to mention that I am reasonably certain Sodium Hyaluronate, being the most common form of Hyaluronic Acid sold, and the only type incorporated into beauty serums, does not penetrate into the skin owing to its high molecular weight of over 1000, making it useless for antiaging purposes, but possibly beneficial for enhancing epidermal wound healing through moisture retention.

Lactic Acid

Lactate delays aging in skin fibroblasts through mitohormesis (ROS-induced cellular protection), and likely many other human cells, making lactic producing exercise such as LAT, Endurance Training, HIT / HIIT systemically and superficially anti-aging.

"<>l-lactate is a natural compound widely used in food and cosmetic industry because of its safety and excellent antimicrobial properties. Moreover, l-lactate levels in human body are intermittently elevated during physical exercise, the condition associated with the prevention of aging-associated diseases and decreased mortality. <>Here, we describe that intermittent treatment of skin fibroblasts with l-lactate levels occurring during exercise causes the mild inhibition of mitochondrial respiratory chain and the increased production of mitochondrial H_2O_2. These effects cause the intermittent shift in the intracellular redox state towards oxidation and trigger the protective and quality control signaling including the phosphorylation of AMPK and the increased transcriptional activity of PGC1α.
<>The long-term intermittent application, but not the constant application, of l-lactate prevents the onset of mitochondrial dysfunction in aged skin fibroblasts, that is, the drop in respiration and the rise of ROS production. The absence of mitochondrial dysfunction in fibroblasts treated with the intermittent l-lactate is associated with the lower activity of mTORC1, the less frequent transition of cells to senescence, and the higher activity of the intracellular quality control by autophagy.
<>In conclusion, the mitohormesis resulting from the intermittent exposure to l-lactate exhibits a potent antiaging effect at least in skin fibroblasts. These results shed a new light on the role of l-lactate in the beneficial effects of physical exercise and in cosmeceutical and nutraceutical preparations."[506.4G]

Adapalene

An over-the-counter acne medication and derivative of Retinoic Acid that appears to reduce photoaging. It is clearly a better product to use for anti-aging purposes than

overpriced and microdosed beauty serums that scam older women through manipulative advertising campaigns.

“<>Background: Adapalene has been previously evaluated as a treatment for actinic keratosis (AK) and solar lentigines and shown to improve signs of photoaging.
<>Objectives: To evaluate whether adapalene 0.3% gel is non-inferior to tretinoin 0.05% cream as treatment for photoaged skin.
<>Materials & methods: An investigator-blinded, parallel-group comparison study was conducted in Brazil. Subjects were randomised in a 1:1 ratio to receive, once daily, adapalene 0.3% gel or tretinoin 0.05% cream. Subjects were evaluated at Weeks 1, 4, 8, 12, 16, 20 and 24, based on clinical signs of cutaneous photoaging, histopathological and digital morphometric findings, as well as safety and tolerability.
<>Results: A comparison of clinical efficacy showed that both treatments did not differ significantly regarding clinical evaluation of the following criteria: global cutaneous photoaging, periorbital wrinkles, ephelides/melanosis, forehead wrinkles, and AK.
<>Conclusion: Adapalene 0.3% gel showed non-inferior efficacy to tretinoin 0.05% cream as treatment for photoaged skin, with a similar safety profile. Adapalene 0.3% gel may therefore be considered a safe and effective option for the treatment of mild or moderate photoaging.”[506.5]

Zinc Oxide Sunscreen

Zinc Oxide is an effective sunscreen and much safer than potentially genotoxic commercial sunscreen chemicals. Zinc works as a sunscreen by absorbing UV photons, and can permeate through the skin, making it a topic antioxidant. It must be mentioned that mineral zinc-based sunscreens are often combined in formulation with Titanium dioxide, which is in my opinion a bad idea to apply topically considering it is neither an antioxidant, nor an essential mineral, therefore you should read your formulation labels carefully.

“<>Background/purpose: The inorganic metal oxide sunscreens titanium dioxide and zinc oxide have been considered to protect against sunburning ultraviolet radiation by physically reflecting/scattering the incident photons and thus protecting the skin. Earlier publications suggested, however, that the primary action of UV protection by these sunscreen agents is through absorption and not by reflection. The purpose of this work was to quantitate the contributions of each of these modes of action to the protection provided by inorganic UV sunscreen filters.
<>Methods: An optical integrating sphere was used to measure the transmission and the reflectance of titanium dioxide and zinc oxide.
<>Results: The average range of reflection for zinc oxide and titanium dioxide throughout the UV range was only 4-5% (less than SPF 2), providing minimal UV protection via this mechanism. The remainder of the UV protection is provided by

semiconductor band gap mediated absorbance of the UV photons. At wavelengths above the semiconductor band gap absorption energy levels (in the long UVA and visible wavelengths), they are predominantly reflectors of light (up to 60% reflection) and non-absorbing.
<>Conclusion: Titanium dioxide and zinc oxide provide UV protection primarily via absorption of UV radiation and not through significant reflection or scattering."[506.6]

Blue Light Exposure

Blue Light emitted from smartphones and computer screens cause ROS generation in facial skin (and eyes), resulting in cellular damage, thereby promoting aging. Humorously, it seems necessary in the 21st century to apply sunscreen every morning, even if we don't exit our homes, and to wear blue light blocking glasses, to mitigate the toxic effects of blue light exposure.

Blue Light isn't merely a toxic wavelength, it does further our evolution by promoting brain activity, and wakefulness, but this comes at the cost of a disturbed circadian rhythm, beyond superficiality. It is strange that for the earliest times on Earth, our species and their ancestors species blue light exposure has come from looking up to the sky, which is made of all visible wavelengths, balanced in nature, and now our blue light exposure is emitted from LED diodes, does that therefore make technology a synthetic sky? I suppose this a metaphysical question that needs to be resolved.

"<>Background: The generation of DNA damage by ultra-violet radiations (UV) is well established, and both the nature of the DNA lesions and their respective DNA repair pathways have largely been described. Besides UV rays, visible light constitutes a very important part of the sun spectrum where blue light is considered a significant contributor to premature aging. However, blue light-induced DNA damage has not been deeply explored yet.
<>Methods: In the present study, we assessed in human skin keratinocytes the DNA and chromosome damaging activities of blue light rays (415 nm) as well as their associated DNA repair mechanisms.
<>Results: Our results demonstrated that blue light induced dose-dependent DNA damage in human keratinocytes. Both oxidative and cyclobutane-pyrimidine-dimer (CPD) DNA lesions were generated. They were repaired through base excision repair (BER) and nucleotide excision repair (NER) pathways, respectively. Moreover, by using the micronucleus assay we demonstrated, for the first time, that a blue wavelength exerted a clastogenic/aneugenic effect in human keratinocytes, leading to chromosome aberration.
<>Conclusion: We concluded that, in normal human keratinocytes, blue light creates genotoxic lesions which might accelerate or at least contribute to premature skin aging."[506.7]

[See: Topically Applied Lipolytic-Myogenic Chemicals: Eucalyptus Globulus oil]

[See: Probiotics, Fibers, & Short Chain Fatty Acids: Amazake / Shio Koji]

[See: Glossary: The main layers of the Skin and their relationship to aging]

Joint Health Supplementation

Nearly all AI supplements & therapies will either halt or reverse arthritis, especially the use of TALM's. But I feel it necessary to include important research on commonly sold joint supplements, some of which are toxic to skeletal muscle and clearly a cause of accelerated musculoskeletal aging, especially in the elderly, who are the primary customers of Joint Health products.

Many joint health supplements exert toxic side effects on skeletal muscle, and metabolism, and should therefore be avoided in favor of the increased intake of vitamins, phytochemicals, and the incorporation of high frequency targeted aerobic resistance exercise into a workout protocol to promote synovial fluid circulation, and even collagen synthesis in cartilage.

The safest and most effective plan for counteracting and preventing arthritis is daily chronic Glycine consumption, which has been correlated to Osteoarthritis development, combined with high frequency, high volume / low load (think IMC Exercise Warmups), exercise to promote enhanced bloodflow to the joints

Glycine

"<>Collagen synthesis is severely diminished in osteoarthritis; thus, enhancing it may help the regeneration of cartilage. This requires large amounts of glycine, proline and lysine. Previous works of our group have shown that glycine is an essential amino acid, which must be present in the diet in large amounts to satisfy the demands for collagen synthesis. Other authors have shown that proline is conditionally essential. <>In this work we studied the effect of these amino acids on type II collagen synthesis. Bovine articular chondrocytes were cultured under a wide range of different concentrations of glycine, proline and lysine. Chondrocytes were characterized by type II collagen immunocytochemistry of confluence monolayer cultures. Cell growth and viability were assayed by trypan blue dye exclusion method. Type II collagen was measured in the monolayer, every 48 h for 15 days by ELISA. Increase in concentrations of proline and lysine in the culture medium enhances the synthesis of type II collagen at low

concentrations, but these effects decay before 1.0 mM. Increase of glycine as of 1.0 mM exceeds these effects and this increase continues more persistently by 60–75%. Since the large effects produced by proline and lysine are within the physiological range, while the effect of glycine corresponds to a much higher range, these results demonstrated a severe glycine deficiency for collagen synthesis.
<>Thus, increasing glycine in the diet may well be a strategy for helping cartilage regeneration by enhancing collagen synthesis, which could contribute to the treatment and prevention of osteoarthritis."[506.8]

Pralmorelin (Growth Hormone Releasing Peptide-2: GHRP-2)

GHRP-2, an inexpensive, legal, & easily purchasable peptide (online) that reduces muscle atrophy factors in muscle & joint tissue, treating arthritis[1]. Importantly, GHRP-6, a chemical that shares some similarity to GHRP-2, promotes lipogenesis, contrary to what is taught in fitness communities, hinting at caution for use of Growth Hormone Releasing Peptides in weight loss scenarios as they may have paradoxical effects in the body, depending on insulin concentrations, and these lipogenic effects of GHRP-6 are likely unrelated to Substrate Competition and moreso to the release of Ghrelin[2].

[1] "<>Chronic arthritis is a catabolic state associated with an inhibition of the IGF system and a decrease in body weight. Cachexia and muscular wasting is secondary to protein degradation by the ubiquitin-proteasome pathway. The aim of this work was to analyze the effect of adjuvant-induced arthritis on the muscle-specific ubiquitin ligases muscle ring finger 1 (MuRF1) and muscle atrophy F-box (MAFbx) as well as on IGF-I and IGF-binding protein-5 (IGFBP-5) gene expression in the skeletal muscle. We also studied whether the synthetic ghrelin receptor agonist, growth hormone releasing peptide-2 (GHRP-2), was able to prevent arthritis-induced changes in the skeletal muscle. Arthritis induced an increase in MuRF1, MAFbx ($P < 0.01$), and tumor necrosis factor (TNF)-alpha mRNA ($P < 0.05$) in the skeletal muscle. Arthritis decreased the serum IGF-I and its gene expression in the liver ($P < 0.01$), whereas it increased IGF-I and IGFBP-5 gene expression in the skeletal muscle ($P < 0.01$).
<>Administration of GHRP-2 for 8 days prevented the arthritis-induced increase in muscular MuRF1, MAFbx, and TNF-alpha gene expression. GHRP-2 treatment increased the serum concentrations of IGF-I and the IGF-I mRNA in the liver and in the cardiac muscle and decreased muscular IGFBP-5 mRNA both in control and in arthritic rats ($P < 0.05$). GHRP-2 treatment increased muscular IGF-I mRNA in control rats ($P < 0.01$), but it did not modify the muscular IGF-I gene expression in arthritic rats.
<>These data indicate that arthritis induces an increase in the activity of the ubiquitin-proteasome proteolytic pathway that is prevented by GHRP-2 administration. The parallel changes in muscular IGFBP-5 and TNF-alpha gene expression with the ubiquitin

ligases suggest that they can participate in skeletal muscle alterations during chronic arthritis."[507.0]

[2] "<>Ghrelin and GH secretagogues, including GH-releasing peptide (GHRP)-6, stimulate food intake and adiposity. Because insulin modulates the hypothalamic response to GH secretagogues and acts synergistically with ghrelin on lipogenesis in vitro, we analyzed whether insulin plays a role in the metabolic effects of GHRP-6 in vivo.
<>Streptozotocin-induced diabetic rats received saline, GHRP-6, insulin, or insulin plus GHRP-6 once daily for 8 wk. Rats receiving saline suffered hyperglycemia, hyperphagia, polydipsia, and weight loss. Insulin, but not GHRP-6, improved these parameters ($P < 0.001$ for all), as well as the diabetes-induced increase in hypothalamic mRNA levels of neuropeptide Y and agouti-related peptide and decrease in proopiomelanocortin. Cocaine amphetamine-related transcript mRNA levels were also reduced in diabetic rats, with GHRP-6 inducing a further decrease ($P < 0.03$) and insulin an increase.
<>Diabetic rats receiving insulin plus GHRP-6 gained more weight and had increased epididymal fat mass and serum leptin levels compared with all other groups ($P < 0.001$). In epididymal adipose tissue, diabetic rats injected with saline had smaller adipocytes ($P < 0.001$), decreased fatty acid synthase (FAS; $P < 0.001$), and glucose transporter-4 ($P < 0.001$) and increased hormone sensitive lipase ($P < 0.001$) and proliferator-activated receptor-γ mRNA levels ($P < 0.01$). Insulin normalized these parameters to control values. GHRP-6 treatment increased FAS and glucose transporter-4 gene expression and potentiated insulin's effect on epididymal fat mass, adipocyte size ($P < 0.001$), FAS ($P < 0.001$), and glucose transporter-4 ($P < 0.05$).
<>In conclusion, GHRP-6 and insulin exert an additive effect on weight gain and visceral fat mass accrual in diabetic rats, indicating that some of GHRP-6's metabolic effects depend on the insulin/glucose status."[507.1]

Methylsulfonylmethane (MSM)

MSM appears to accumulate in the body over time and may therefore be a supplement to cycle off of for longer periods, such as six-twelve months per year.

[A] MSM enhances GH signaling in bones.

"<>Methylsulfonylmethane is a naturally occurring sulfur compound with well-known anti-oxidant properties and anti-inflammatory activities. But its effects on bone are unknown. Growth hormone (GH) is regulator of bone growth and bone metabolism. GH activates several signaling pathways such as the Janus kinase (Jak)/signal transducers and activators of transcription (STAT) pathway, thereby regulating expression of genes

including insulin-like growth factor (IGF)-1. GH exerts effects both directly and via IGF-1, which signals by activating the IGF-1 receptor (IGF-1R).
<>In this study, we investigated the effects of MSM on the GH signaling via the Jak/STAT pathway in osteoblasts and the differentiation of primary bone marrow mesenchymal stem cells (MSCs). MSM was not toxic to osteoblastic cells and MSCs. MSM increased the expression of GH-related proteins including IGF-1R, p-IGF-1R, STAT5b, p-STAT5b, and Jak2 in osteoblastic cells and MSCs. MSM increased IGF-1R and GHR mRNA expression in osteoblastic cells. The expression of MSM-induced IGF-1R and GHR was inhibited by AG490, a Jak2 kinase inhibitor. MSM induced binding of STAT5 to the IGF-1R and increased IGF-1 and IGF-1R promoter activities. Analysis of cell extracts by immunoprecipitation and Western blot showed that MSM enhanced GH-induced activation of Jak2/STAT5b.
<>We found that MSM and GH, separately or in combination, activated GH signaling via the Jak2/STAT5b pathway in UMR-106 cells. Using siRNA analysis, we found that STAT5b plays an essential role in GH signaling activation in C3H10T1/2 cells. Osteogenic marker genes (ALP, ON, OCN, BSP, OSX, and Runx2) were activated by MSM, and siRNA-mediated STAT5b knockdown inhibited MSM-induced expression of osteogenic markers. Furthermore, MSM increased ALP activity and the mineralization of MSCs. Taken together, these results indicated that MSM can promote osteogenic differentiation of MSCs through activation of STAT5b."[507]

[B] MSM might protect skeletal muscle against cortisol.

"<>Cortisol is a hormone involved in stress during exercise. The application of natural compounds is a new potential approach for controlling cortisol-induced stress. Tumour suppressor protein p53 is activated during cellular stress. Succinate dehydrogenase complex subunit A (SDHA) and hypoxanthine phosphoribosyl transferase 1 (HPRT1) are considered to be two of the most stable reference genes when measuring stress during exercise in horses.
<>In the present study cells were considered to be in a 'stressed state' if the levels of these stable genes and the highly stress responsive gene p53 were altered. It was hypothesized that a natural organic sulphur-containing compound, methylsulfonylmethane (MSM), could inhibit cortisol-induced stress in racing horse skeletal muscle cells by regulating SDHA, HPRT1 and p53 expression. After assessing cell viability using MTT assays, 20 μg/ml cortisol and 50 mM MSM were applied to horse skeletal muscle cell cultures. Reverse transcription-quantitative PCR and western blot analysis demonstrated increases in SDHA, HPRT1 and p53 expression in cells in response to cortisol treatment, which was inhibited or normalized by MSM treatment. To determine the relationship between p53 and SDHA/HPRT1 expression at a transcriptional level, horse gene sequences of SDHA and HPRT1 were probed to identify novel binding sites for p53 in the gene promoters, which were confirmed using a chromatin immunoprecipitation assay. The relationship between p53 and SDHA/HPRT1 expression

was confirmed using western blot analysis following the application of pifithrin-α, a p53 inhibitor. These results suggested that MSM is a potential candidate drug for the inhibition of cortisol-induced stress in racehorse skeletal muscle cells."[508]

Hyaluronic Acid (Hyaluronan)

[A] HA is orally bioavailable, and when orally administered is distributed to the skin, & most likely also to the joints.

"Hyaluronan (HA) has been utilized as a supplement. However, the absorption of orally administrated HA remains controversial. The degradation and absorption of HA in the intestine were investigated in this study. HA excretion into the feces, degradation in the intestinal tract, absorption through the large intestine, and translocation to the blood and skin were examined. HA administered orally was not detected in rat feces. HA was degraded by cecal content, but not by artificial gastric juice and intestinal juice. Oligosaccharide HA passed through excised large intestine sacs. Furthermore, disaccharides, tetrasaccharides, and polysaccharides HA were distributed to the skin of rats following oral administration of high molecular weight HA (300 kDa). The results of the study suggest that orally administered HA is degraded to oligosaccharides by intestinal bacteria, and oligosaccharide HA is absorbed in the large intestine and is subsequently distributed throughout the tissues, including the skin."[509]

[B] HA is myogenic through promoting differentiation.

"<>Exogenous hyaluronan is known to alter muscle precursor cell proliferation, migration, and differentiation, ultimately inhibiting myogenesis in vitro. The aim of the current study was to investigate the role of endogenous hyaluronan synthesis during myogenesis. In quantitative PCR studies, the genes responsible for synthesizing hyaluronan were found to be differentially regulated during muscle growth, repair, and pathology. Although all Has genes (Has1, Has2, and Has3) were differentially regulated in these models, only Has2 gene expression consistently associated with myogenic differentiation. During myogenic differentiation in vitro, Has2 was the most highly expressed of the synthases and increased after induction of differentiation. To test whether this association between Has2 expression and myogenesis relates to a role for Has2 in myoblast differentiation and fusion, C2C12 myoblasts were depleted of Has2 by siRNA and induced to differentiate. Depletion of Has2 inhibited differentiation and caused a loss of cell-associated hyaluronan and the hyaluronan-dependent pericellular matrix.
<>The inhibition of differentiation caused by loss of hyaluronan was confirmed with the hyaluronan synthesis inhibitor 4-methylumbelliferone. In hyaluronan synthesis-blocked cultures, restoration of the pericellular matrix could be achieved through the addition of exogenous hyaluronan and the proteoglycan versican, but this was not sufficient to restore differentiation to control levels.

<>These data indicate that intrinsic hyaluronan synthesis is necessary for myoblasts to differentiate and form syncytial muscle cells, but the hyaluronan-dependent pericellular matrix is not sufficient to support differentiation alone; additional hyaluronan-dependent cell functions that are yet unknown may be required for myogenic differentiation."[510]

Glucosamine

[A] Glucosamine is simply an anti-inflammatory agent, by reducing IL-6, and TNF-a, it can treat arthritis, however this anti-inflammatory effect is unimpressive, and can be achieved through the use of different phytochemicals, or ideally, the chronic daily application of Essential oils to damaged joints.

"This study analysed the effects of different doses of glucosamine hydrochloride (GS-HCl) on cartilage tissue and the levels of joint injury markers in knee osteoarthritis (KOA). The Sham group, KOA group, low-dose GS-HCl group and high-dose GS-HCl group were established, with six mice in each group. The levels of joint injury markers (COMP, CS846 and CTX-II), inflammatory cytokines (IL-6, TNF-α and iNOS), oxidative stress indicators (MDA and SOD) and matrix remodelling proteins (MMP-3 and TIMP-1) were analysed. The degeneration of knee femoral condyles, histopathological changes and tissue apoptosis rate of the articular cartilage was also assessed. Mice in the KOA group displayed elevated COMP, CS846, CTX-II, IL-6, TNF-α, iNOS and MDA contents, reduced SOD activity, an irregular articular cartilage surface, a serious cartilage defect, a disordered articular cartilage surface in the defect, disappeared cartilage cells, obvious synovial cell proliferation and visible inflammatory cell infiltration. In the tissue, apoptosis rate and MMP-3 and TIMP-1 protein expression increased. Different doses of GS-HCl treatment could reduce COMP, CS846, CTX-II, IL-6, TNF-α, iNOS and MDA contents, apoptosis rate and MMP-3 and TIMP-1 protein expression, increase SOD activity and improve histopathological conditions in KOA mice. The improvement effects in each indicator in the high dose-GS-HCl group were more significant than those in the low dose-GS-HCl group. The intragastric administration of the GS-HCl group partially prevents the degeneration of articular cartilage in KOA mice. The mechanism may be to reduce inflammatory factors and oxidative stress indicator expression and matrix degradation, thereby delaying osteoarthritis progression."[510.1]

[B] Glucosamine stimulates lipid accumulation in muscle through PPARy and causes Insulin Resistance, proving quite clearly that some joint health supplements may unintendedly accelerate physiological aging (if a diet is not monitored carefully).

"<>Hyperglycemia-induced activation of hexosamine biosynthesis pathway (HBP) has been implicated in the development of insulin resistance in skeletal muscles. In the present study, the content of uridine-5'-diphospho-N-acetylglucosamine, the end product of the HBP, was elevated in skeletal muscle of obese diabetic KKA(y) mice, compared

with control mice. To elucidate the effect of elevated HBP in the skeletal muscle, we treated C2C12 myoblasts with glucosamine, an intermediate metabolite of the HBP. Glucosamine induced lipid accumulation and significantly increased the mRNA expression levels of peroxisome proliferator-activated receptor gamma, adiponectin, and aP2 in C2C12 myoblasts. Similar mRNA changes were observed in skeletal muscles of Sprague-Dawley rats treated with glucosamine infusion. Our results provide a possible explanation of hyperglycemia-induced insulin resistance in skeletal muscle."[511]

Chondroitin

Chondroitin halts myogenic differentiation 1.

[A] "<>Chondroitin sulfate (CS), a type of glycosaminoglycan (GAG), is a factor involved in the suppression of myogenic differentiation. CS comprises two repeating sugars and has different subtypes depending on the position and number of bonded sulfate groups. However, the effect of each subtype on myogenic differentiation remains unclear. In this study, we spiked cultures of C_2C12 myoblasts, cells which are capable of undergoing skeletal muscle differentiation, with one of five types of CS and induced differentiation over a fixed time. After immunostaining of the formed myotubes with an anti-MHC antibody, we counted the number of nuclei in the myotubes and then calculated the fusion index (FI) as a measure of myotube differentiation.
<>Collectively, it can be concluded that the degree of suppression of differentiation depends on the subtype of CS and that CS-E strongly suppresses myogenic differentiation. We conclude that the CS sugar chain has inhibitory action against myoblast cell fusion."[512]

[B] Chondroitin halts myogenic differentiation 2. Decreasing muscular chondroitin levels may be a future myogenic therapy.

"<>Skeletal muscle formation and regeneration require myoblast fusion to form multinucleated myotubes or myofibers, yet their molecular regulation remains incompletely understood. We show here that the levels of extra- and/or pericellular chondroitin sulfate (CS) chains in differentiating C2C12 myoblast culture are dramatically diminished at the stage of extensive syncytial myotube formation. Forced down-regulation of CS, but not of hyaluronan, levels enhanced myogenic differentiation in vitro. This characteristic CS reduction seems to occur through a cell-autonomous mechanism that involves HYAL1, a known catabolic enzyme for hyaluronan and CS. In vivo injection of a bacterial CS-degrading enzyme boosted myofiber regeneration in a mouse cardiotoxin-induced injury model and ameliorated dystrophic pathology in mdx muscles.
<>Our data suggest that the control of CS abundance is a promising new therapeutic approach for the treatment of skeletal muscle injury and progressive muscular dystrophies."[512.0]

[See: Topically Applied Myogenic-Lipolytic chemicals]

Photobiomodulation Therapy

Research is beginning to show the benefits of LED light therapy, especially *Green* LED light. From enhancing IGF-1 production & muscle hypertrophy, to accelerating wound healing (angiogenesis) and promoting collagen formation, this novel therapy is very promising. The wavelength is described as "nm". Do not assume you need to purchase an overpriced professional light therapy device, or "LED Bed" to experiment with this new science, for myogenic ends a better idea is to purchase a long section of dual row LED strip, Green or Red, and wrap it around your body, especially limbs[G], for an hour or more every day, especially post-angiogenic exercise.

I feel it is important to clarify I do not believe LED light therapy is the most effective topically administered antiaging therapy because even though light emitting diode waves appear to promote collagen synthesis in the epidermis and dermis (skin) likely by promoting Mitohormesis, they also promote angiogenesis, and unknown levels of ROS. Therefore, it is logical to infer that with repeated, and possibly abused LED therapy on human faces, facial blood vessel growth will increase to the point at which the new blood vessels are noticeable and will, similar to wrinkling, detract from "beauty standards", and with the increased production of ROS, skin cancer risk will substantially increase when paired with UV Radiation, or systemic inflammation. Therefore, Photobiomodulation therapy is much more suited to enhance angiogenesis and promote myogenesis, rather than to reverse or delay superficial aging, whereas it makes far more sense to me to quell ROS production in the skin through the use of TALM's, but this is only my analytical opinion.

In closing, I must also mention that I do not think LED light emitted from a distant source such as will be commonplace with commercial Photobiomodulation Therapy devices or beds will exert as much of an angiogenic effect as from cheaply purchased LED strips wrapped directly around our bare skin.

[A] EMF (Infrared) Wavelengths do little to enhance wound healing, whereas wounds exposed to Red LED light (LED-RL) display accelerated healing.

"The aim of the present study was to evaluate the in vivo response of different wavelengths (red and near-infrared) of light-emitting diode (LED) on full-thickness skin grafts (FTSG) in rats. Thirty rats were randomly allocated into three experimental groups: control group (C); red LED treated group (R); and near-infrared LED group (NIR). Skin grafts were irradiated daily for ten consecutive days, starting immediately after the surgery using a red (630 nm) or near-infrared (850 nm) LED. The results showed that the red wavelength LED significantly enhanced the skin graft score in relation to the NIR group and increased transforming growth factor beta (TGF-β) protein expression and

density of collagen fibers compared with the other experimental groups. These results suggest that the red wavelength LED was efficient to improve the dermo-epidermal junction and modulate the expression proteins related to tissue repair."[512.1]

[B] Red & Green LED light exposure enhances angiogenesis, with Green LED showing a much greater effect.

"<>Low level light therapy receives increasing interest in the fields of tissue regeneration and wound healing. Several *in vivo* studies demonstrated the positive effects of LLLT on angiogenesis. This study aimed to investigate the underlying properties *in vitro* by comparing the effects of light therapy by light emitting diodes of different wavelengths on endothelial cells *in vitro*. Human umbilical vein endothelial cells were treated with either 475 nm, 516 nm or 635 nm light. Control cells were not illuminated. 2D proliferation was quantified by manual counting. HUVEC migration was analyzed by performing a 2D wound scratch assay and a 3D bead assay.
<>The influence of LLLT on early vasculogenic events was determined in a 3D fibrin co-culture model with adipose-derived stem cells. Stimulation with both red and green pulsed LED light significantly increased HUVEC proliferation and 3D migration. Moreover, HUVEC showed increased 2D migration potential with green light stimulation. The treatment with blue light was ineffective.
<>Several parameters showed that green light was even more potent to stimulate proliferation and migration of endothelial cells than clinically well-established red light therapy. Further studies have to focus on intracellular mechanisms induced by different wavelengths in order to optimize this promising therapy in tissue regeneration."[512.2]

[B2] Green LED therapy enhances angiogenesis 2.

"<>Because light-emitting diodes (LEDs) are low-coherent, quasimonochromatic, and nonthermal, they are an alternative for low level laser therapy, and have photobiostimulative effects on tissue repair. However, the molecular mechanism(s) are unclear, and potential effects of blue and/or green LEDs on wound healing are still unknown.
<>Here, we investigated the effects of red (638 nm), blue (456 nm), and green (518 nm) LEDs on wound healing. In an in vivo study, wound sizes in the skin of ob/ob mice were significantly decreased on day 7 following exposure to green LEDs, and complete reepithelialization was accelerated by red and green LEDs compared with the control mice. To better understand the molecular mechanism(s) involved, we investigated the effects of LEDs on human fibroblasts in vitro by measuring mRNA and protein levels of cytokines secreted by fibroblasts during the process of wound healing and on the migration of HaCat keratinocytes.
<>The results suggest that some cytokines are significantly increased by exposure to LEDs, especially leptin, IL-8, and VEGF, but only by green LEDs. The migration of HaCat keratinocytes was significantly promoted by red or green LEDs. In conclusion, we

demonstrate that green LEDs promote wound healing by inducing migratory and proliferative mediators, which suggests that not only red LEDs but also green LEDs can be a new powerful therapeutic strategy for wound healing."[512.3]

[C] Green LED therapy enhances MRF production and stem cell activity thereby promoting muscle hypertrophy. Whether LED light can pierce through the epidermis and adipose tissue, and reach the muscle tissue is up for debate. But I believe it depends on the distance of the LED light emission from the skin, See [G].

"<>Previous studies showed that monochromatic green light stimuli during embryogenesis accelerated posthatch body weight (BW) and pectoral muscle growth of broilers. In this experiment, we further investigated the morphological and molecular basis of this phenomenon. Fertile broiler eggs (Arbor Acres, n=880) were pre-weighed and randomly assigned to 1 of the 2 incubation treatment groups: (1) dark condition (control group), and (2) monochromatic green light group (560 nm). The monochromatic lighting systems sourced from light-emitting diode lamps and were equalized at the intensity of at eggshell level. The dark condition was set as a commercial control from day 1 until hatching. After hatch, 120 male 1-day-old chicks from each group were housed under incandescent white light with an intensity of 30 lx at bird-head level. <>No effects of light stimuli during embryogenesis on hatching time, hatchability, hatching weight and bird mortality during the feeding trial period were observed in the present study. Compared with the dark condition, the BW, pectoral muscle weight and myofiber cross-sectional areas were significantly greater on 7-day-old chicks incubated under green light. Green light also increased the satellite cell mitotic activity of pectoral muscle on 1- and 3-day-old birds. In addition, green light upregulated MyoD, myogenin and myostatin mRNA expression in late embryos and/ or newly hatched chicks. <>These data suggest that stimulation with monochromatic green light during incubation promote muscle growth by enhancing proliferation and differentiation of satellite cells in late embryonic and newly hatched stages. Higher expression of myostatin may ultimately help prevent excessive proliferation and differentiation of satellite cells in birds incubated under green light."[512.4]

[D] Red LED (LED-RL) penetrates the skin to a greater degree than Green due to its wavelength, and Red LED promotes wound healing by activating nitric oxide and ROS, thereby promoting inflammation. Remember, any inflammatory modality or chemical has the chance of causing cancer and accelerating aging, and this means Photobiomodulation Therapy may accelerate skin aging if used in excess.

"<>[The] Theoretical mechanism of LED red light photobiomodulation. 1 Light has optimal tissue penetration when its wavelength is within the "optical window," (600–1070 nm). Red light (620–750 nm) takes advantage of this penetration window. 2 LED-RL stimulates the photo-acceptor copper complex in cytochrome C oxidase, stimulating the photodissociation of nitric oxide (NO), leading to upregulation of the electron

transport chain. This stimulation of the electron transport leads to the following intramitochondrial changes: increased generation of ATP and reactive oxygen species (ROS)"[512.5]

[E] Red LED enhances skin collagen production and reduces visible signs of aging. Do not be fooled by the term "Deep Red" it is merely a marketing term.

"<>Light-emitting diodes (LEDs) are considered to be effective in skin rejuvenation. We investigated the clinical efficacy of LED phototherapy for skin rejuvenation through the comparison with three different treatment parameters and a control, and also examined the LED-induced histological, ultrastructural, and biochemical changes. Seventy-six patients with facial wrinkles were treated with quasimonochromatic LED devices on the right half of their faces. All subjects were randomly divided into four groups treated with either 830nm alone, 633nm alone, a combination of 830 and 633nm, or a sham treatment light, twice a week for four weeks. Serial photography, profilometry, and objective measurements of the skin elasticity and melanin were performed during the treatment period with a three-month follow-up period. The subject's and investigator's assessments were double-blinded. Skin specimens were evaluated for the histologic and ultrastructural changes, alteration in the status of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs), and the changes in the mRNA levels of IL-1ss, TNF-alpha, ICAM-1, IL-6 and connexin 43 (Cx43), by utilizing specific stains, TEM, immunohistochemistry, and real-time RT-PCR, respectively.
<>In the results, objectively measured data showed significant reductions of wrinkles (maximum: 36%) and increases of skin elasticity (maximum: 19%) compared to baseline on the treated face in the three treatment groups. Histologically, a marked increase in the amount of collagen and elastic fibers in all treatment groups was observed. Ultrastructural examination demonstrated highly activated fibroblasts, surrounded by abundant elastic and collagen fibers. Immunohistochemistry showed an increase of TIMP-1 and 2. RT-PCR results showed the mRNA levels of IL-1ss, TNF-alpha, ICAM-1, and Cx43 increased after LED phototherapy whereas that of IL-6 decreased. This therapy was well-tolerated by all patients with no adverse effects. We concluded that 830 and 633nm LED phototherapy is an effective approach for skin rejuvenation."[512.6]

[F] As an addendum. Blue Light Therapy appears to enhance cognition, beyond its well-known tendency to reduce melatonin secretion. This would explain why most people find it so difficult to maintain a sleep schedule after using their technological device of choice before bed, as brain activity is meant to slow in the evening hours.

"<>Objective: Blue light is a powerful environmental stimulus that can produce significant phase shifts in the circadian rhythm of melatonin and sleep propensity as well as acute effects on alertness of neurobehavioral performance. Here, we undertook an expansion and reanalysis of our previously published findings to examine the effect of acute blue light exposure on the strength of resting-state functional connectivity (rsFC)

between a previously identified region of the left dorsolateral prefrontal cortex (DLPFC) and 106 cortical and subcortical regions.
<>Methods: Twenty-nine healthy adults (16 men and 13 women; age 18-32 years) completed a psychomotor vigilance test (PVT) before and after a single 30-min exposure to either blue (λ = 469 nm; n = 17) or amber wavelength (λ = 578 nm; n = 12) light, immediately followed by an rsFC scan.
<>Results: Compared with amber light, blue light exposure produced significantly greater functional connectivity between the left DLPFC seed region and 30 cortical and subcortical regions ($P < 0.05$; false discovery rate-corrected). Although neurobehavioral performance did not differ between light conditions, only those exposed to blue light showed a significant association between rsFC and sustained PVT performance. Better sustained PVT performance was associated with greater connectivity between the left DLPFC and regions associated with visuospatial awareness/motion detection (right temporal-occipital middle temporal gyrus) and memory (left hippocampus), as well as reduced connectivity in a circuit associated with cognitive rumination and distraction (left parahippocampal gyrus).
<>Conclusion: Findings suggest that blue-wavelength light may facilitate acute alertness and improved cognitive performance through enhanced rsFC between the left DLPFC and cortical regions associated with visuospatial awareness.”[512.7]

[G]

Aromatherapy, Phytoncides, & Forest Bathing

Most plant life, specifically trees, leaves, and grass, release aromatic pesticide compounds (Volatile Organic Compounds: VOC's) called Phytoncides. Essential Oils (EO) are especially pungent and ancient plant extracts used as incense, for ceremonial purposes. The aromatic compounds within EO's are capable of altering brain waves, promoting neurotrophic factors, or acting as immunomodulators. In the 1980s the Japanese created a therapy called "Forest Bathing", in which simply explained, someone exposes themselves to as many VOC's as possible by "bathing" in the aromatic air of the forest for the promotion of overall health.

I will be primarily discussing the benefits of two primary VOC's as they have low POP & high availability. If it isn't obvious to you, aromatherapy and TALM's should be used only on an Anti-Inflammation Cycle as I estimate 95%$^{+}$ of phytochemicals suppress

angiogenesis. As a warning, Linalool is estrogenic and should not be used by men either topically or orally, unless they are of *very low body fat* to avoid gynecomastia developing, whereas women should use it, as estrogen is their antiaging compatriot.

Essential oils can be better utilized when understood and classified as *Sedating* or *Stimulating* i.e. Essential oils that contain phytochemicals that reduce brain activity thereby promoting relaxation, or ones that stimulate brain activity thereby promoting wakefulness or cognition. Puzzlingly, most Essential oils have been shown to possess anticonvulsant-inhibitory activity, and I can't classify EO's by pharmacodynamics alone, such as by GABAergic – Serotoninergic – Dopaminergic acting VOC's, because subtle (not strong) neurotransmitter changes tend to effect each individual differently. Regardless, I have formulated *subjective* Sedating / Stimulating EO classification lists you can start with, but I would strongly recommend that you test every Essential oil you have access to individually and with an open mind, without other variables, and journal the affects you experience after extended and repeated direct nasal inhalation, which should allow you ample opportunity to self-classify each essential oil into one of two (or more) categories as previously mentioned. After you have a few EO's classified you can begin mixing them into blends to create potent synergies. Once you have created enough subjective classifications of EO's, this will allow you to time-restrict EO's and EO Blends to morning and evening hours, work and procrastination hours, and even happy and unhappy hours as examples, thus propelling you towards mastering the *scents and sciences* of Psychoaromatherapy.

It must be mentioned that EO VOC's are extremely potent, and even short duration inhalation is liable to cause noticeable change to blood and brain chemistry, it is unwise to expose a healthy child to potent, if but natural, aromatic compounds, as this exposure could result in hormonal changes that go unnoticed, such as the estrogenic VOC Linalool found in Lavender oils that may cause gynecomastia in boys or premature breast growth in girls. It is best to save your aromatherapy experimentation for yourself, or other adults. In the event that your child displays psychological abnormalities, such as depression, learning difficulties, or anger issues, and his or her environment is stable (i.e. you are not the cause of their suffering), then it may be necessary and therapeutic to use EO's to soothe their psyches. As long as the oils you expose them to are not strong phytoestrogens, and are not excitatory compounds (Cineole), the child's mental state should improve following aromatherapy. In my opinion, "Woody / Woodsy" + Floral EO blends are good starting points for childhood aromatherapy.

IMC Sedating Essential oils (Floral, Sweet, Woodsy): Lavender oil, Sandalwood oil, Cedarwood oil, Hop oil, Chamomile oil, Valerian oil, Ylang-ylang oil, Rose oil, Sage oil, Jasmine oil, Geranium oil, Frankincense oil, Myrrh oil.

IMC Stimulating Essential oils (Fresh, Pungent, Spicy): Eucalyptus Globulus oil, Rosemary oil, Thyme oil, Black Pepper oil, Cinnamon oil, Clove oil, Peppermint oil, Lemon oil, Orange oil, Grapefruit oil, Pine oil, Juniper Berry oil, Ginger oil.

The question presents itself: To what part did Phytoncides play in our evolution?

[A] Forest Bathing reduces cortisol.

"<>Forest bathing is a traditional practice characterized by visiting a forest and breathing its air. This review aims to investigate the effects of forest bathing on levels of salivary or serum cortisol as a stress biomarker in order to understand whether forest bathing can reduce stress. Medline/PubMed, Embase, Scopus, Web of Science, Cochrane Library, and Google Scholar were systematically searched for relevant articles. The quality of included trials was assessed following the criteria of the NIH dedicated tools. Afterwards, a qualitative and quantitative synthesis of retrieved evidence was performed. A total of 971 articles were screened; 22 of them were included in the systematic review and 8 in the meta-analysis. In all but two included studies, cortisol levels were significantly lower after intervention in forest groups if compared with control/comparison groups, or a significant pre-post reduction of cortisol levels was reported in the forest groups. <>The main results of the meta-analysis showed that salivary cortisol levels were significantly lower in the forest groups compared with the urban groups both before (MD = - 0.08 μg/dl [95% CI - 0.11 to - 0.05 μg/dl]; $p < 0.01$; $I2 = 46\%$) and after intervention (MD = - 0.05 μg/dl [95% CI - 0.06 to - 0.04 μg/dl]; $p < 0.01$; $I2 = 88\%$). Overall, forest bathing can significantly influence cortisol levels on a short term in such a way as to reduce stress, and anticipated placebo effects can play an important role in it. Further research is advised because of the limited available data."[513]

[B] Forest Bathing enhances the immune system, specifically Natural Killer (NK) (Cancer Killing) cells.

"<>In order to explore the effect of forest bathing on human immune function, we investigated natural killer (NK) activity; the number of NK cells, and perforin, granzymes and granulysin-expression in peripheral blood lymphocytes (PBL) during a visit to forest fields. Twelve healthy male subjects, age 37-55 years, were selected with informed consent from three large companies in Tokyo, Japan. The subjects experienced a three-day/two-night trip in three different forest fields. On the first day, subjects walked for two hours in the afternoon in a forest field; and on the second day, they walked for two hours in the morning and afternoon, respectively, in two different forest fields. Blood was sampled on the second and third days, and NK activity; proportions of NK, T cells, granulysin, perforin, and granzymes A/B-expressing cells in PBL were measured. Similar measurements were made before the trip on a normal working day as the control.

<>Almost all of the subjects (11/12) showed higher NK activity after the trip (about 50 percent increased) compared with before. There are significant differences both before and after the trip and between days 1 and 2 in NK activity. The forest bathing trip also significantly increased the numbers of NK, perforin, granulysin, and granzymes A/B-expressing cells. Taken together, these findings indicate that a forest bathing trip can increase NK activity, and that this effect at least partially mediated by increasing the number of NK cells and by the induction of intracellular anti-cancer proteins."[514]

[C] Two aromatic chemicals found in leaves and grass (Green Odor) promote bDNF expression. Why pay the premium for EO's when you could create your own Aromatic Nootropic blend by collecting leaves and grass from the nature surrounding you, extracting the oils with a DIY-method, and adding them to your oil diffuser?

"<>It is widely accepted that mental stress is an important factor in the development of psychological disorders such as depression. On pre-existing evidence, the so-called green odor may have a relieving and sedative effect on animals exposed to stressful situations. Using two behavioral models of depression, the forced-swim test and learned helplessness paradigm, we investigated whether inhalation of green odor (a 50:50 mixture of trans-2-hexenal and cis-3-hexenol) might alleviate and/or prevent experimentally induced depressive-like states in rats. A 3-min swim every day for 7 days resulted in significant prolongation of immobility time (vs. day 1).
<>Inhaling green odor, but not vehicle, thereafter for 10 days (without swimming) led to the prolonged immobility time being significantly reduced and the hippocampal level of brain-derived neurotrophic factor (BDNF) being significantly increased. In the learned helplessness paradigm, the failure number and time spent in the shock compartment seen in the active avoidance test were both significantly attenuated in those rats that inhaled green odor for 11 days after the postshock screening test (vs. vehicle-exposed rats).
<>Finally, for 10 consecutive days rats continuously exposed to green odor or vehicle swam for 3 min/day. Immobility time was significantly shorter in the green-odor group than in the vehicle-exposed group on days 6-10. These results suggest that green odor has not only a therapeutic, but also a preventive effect on depressive-like states in rats. These effects may be at least in part due to a green odor-induced upregulation of BDNF in the hippocampus."[515]

[D] Quercus ilex (Evergreen Oak) absorbs a great amount of airborne contaminates[1], including airborne metals[2]. Is it time to bring a few into our homes?

[D2] "A number of studies have focused on urban trees to understand their mitigation capacity of air pollution. In this study particulate matter (PM) deposition on Quercus ilex leaves was quantitatively analyzed in four districts of the City of Terni (Italy) for three periods of the year. Fine (between 0.2 and 2.5 μm) and Large (between 2.5 and 10 μm) PM fractions were analyzed. Mean PM deposition value on Quercus ilex leaves was 20.6 μg cm−2. Variations in PM deposition correlated with distance to main roads and

downwind position relatively to industrial area. Epicuticular waxes were measured and related to accumulated PM. For Fine PM deposited in waxes we observed a higher value (40% of total Fine PM) than Large PM (4% of total Large PM). Results from this study allow to increase our understanding about air pollution interactions with urban vegetation and could be hopefully taken into account when guidelines for local urban green management are realized."[515.1]

[D3] "<>The study of particulate matter pollution in urban areas is of great concern due its adverse effects on human health. Roadside vegetation, intercepting and filtering it, contributes to improve air quality. The aim of the research was to investigate the capability of Q. ilex leaves, already known good biomonitors of air quality, in filtering air metals. Besides, the main derivation (i.e. air or root uptake) of the investigated metals in leaf tissue was evaluated. The concentrations of Cd, Cr, Cu, Ni and Pb were measured in three groups of Q. ilex leaves (unwashed, water washed and chloroform washed). Besides, several leaf traits (i.e. length, width, petiole length, leaf area, leaf mass area and thickness) were evaluated. The findings highlighted that Cd, Cr, Cu, Ni and Pb in Q. ilex leaves exceeded the chemical fingerprint.
<>In particular, Cd and Pb appeared the main contaminants of the investigated area as also after water washing of the leaves, their concentrations exceeded the chemical fingerprint. Ni, Cr and Pb appeared to be accumulated on leaf deposit; whereas, Cd appeared mainly adsorbed to leaf cuticle. Higher leaf width, lower leaf area and shorter petiole favoured leaf metal accumulation. Root uptake and translocation to leaves cannot be excluded for Cr and Ni; whereas, leaf Cu content would seem to depend on both leaf deposit and soil content. In conclusion, Q. ilex can be useful in filtering air metal pollution, especially for Ni, Cd, Cr and Pb, and improving air quality."[515.2]

1,8-Cineole & Linalool

In my opinion these are the two most potent, and when inhaled—safest EO-derived nootropic VOC's. Cineole is excitatory, whereas Linalool is inhibitory. Eucalyptus Globulus is the highest bearer of 1,8-cineole, whereas Lavender Angustifolia is my favorite source of Linalool, and Lavender Latifolia is my favorite combined source of both. As for Cineole (also known as Eucalyptol), it was Shakespeare who wrote in Hamlet "Ophelia: There's rosemary, that's for *remembrance*." (Cineole is a major chemical component of Rosemary oil).

"<>Several studies have shown the influence of fragrances on attentional functions and affective state in humans. The present study aimed to investigate the effects of the monoterpenoid compounds 1,8-cineole and (–)-linalool on the neuronal substrate of working memory, cognitive performance, physiological arousal, and affect. To this end, brain activation was assessed using functional magnetic resonance imaging (fMRI) in 69

young healthy adults while they performed a 1-back task during inhalation or dermal application of one of the fragrances.
<>The functional activation data of 51 subjects were included in the statistical analysis. Each condition was compared with an appropriate placebo condition without any fragrances. In addition, heart rate and respiration rate were measured. Before and after fMRI, affective state was assessed by means of rating scales.
<>The results showed significant functional changes in brain areas related to working memory as a function of both fragrance and administration. Specifically, relative to placebo dermal application of 1,8-cineole increased brain activation in the frontal cortex, whereas dermal (–)-linalool increased cerebral blood flow in the basal ganglia. However, no such changes were observed after inhalation. In addition, dermal (–)-linalool decreased error rate in the working memory task, while 1,8-cineole did not

affect performance. No effects of fragrance administration were detected on physiological arousal or affective state. These findings demonstrate that fragrances differentially affect brain activation and working memory in humans and emphasize the importance of the mode of administration when studying the effects of odorants on human cognition."[516]

Ultrasonic Diffusers release more VOC's when the oils are paired with tap water.

"<>Ultrasonic essential oil diffusers (EODs) are a popular type of indoor scenting source. We performed a chamber study in which we measured the emissions from EODs used with lemon, lavender, eucalyptus, and grapeseed oils. Over the course of 15 min, the most abundant VOCs released from lemon, lavender, eucalyptus, and grapeseed oils were 2.6 ± 0.7 mg of d-limonene, 3.5 ± 0.4 mg of eucalyptol, 1.0 ± 0.1 mg of linalyl acetate, and 0.2 ± 0.02 mg of linalyl acetate, respectively. Each oil had a unique particulate matter (PM) emission profile in terms of size, number density, and rate. The dominant size ranges of the PM were 10-100 nm for lemon oil, 50-100 nm for lavender oil, 10-50 nm for lemon oil, and above 200 nm for grapeseed oil. PM1 emission rates of approximately 2 mg/h, 0.1 mg/h, and 3 mg/h, were observed for lemon, lavender/eucalyptus, and grapeseed oils, respectively.
<>A fivefold increase in PM1 emission was measured when the EOD with eucalyptus oil was filled with tap water as opposed to deionized water. Modeling suggests that reasonable use cases of EODs can contribute substantially to primary and secondary PM in indoor environments, but this potential varies depending on the oil and water types used."[517]

Linalool

It appears that Linalool has little benefit and in fact may pose detrimental neurological effects to those without psychological stress (by reducing Nerve Growth Factor in unstressed animals), but this shouldn't be an issue for a modern human being, and may

even treat Alzheimer's Disease. Furthermore, it is a hypothesis of mine that Linalool is an excellent substance towards counteracting caffeine-induced anxiety. Adding one drop of Lavender oil to your coffee or caffeinated beverage, especially if you are a female, is an interesting idea, not only to achieve anxiolysis, but to stimulate the estrogen receptors. As for the safety of oral Linalool, Cilantro has a high concentration of Linalool and is added to Salsa's and other foods frequently, alas with the advent of Lavender Coffee drinks so too shall gynecomastia lawsuits follow.

"Inhalation of various essential oils elicits behavioral changes as a consequence of a complex centrally coordinated response. To understand the molecular mechanisms of action of aromatic compounds on emotional responses, we evaluated the stress-induced changes in mouse brain and the efficacy of inhaled essential oil from Lavandula officinalis (LvEO) using two approaches: a behavioral test, and examining the expression levels of selected genes {fast nerve growth factor receptor (NGFR) mRNA, activity regulated cytoskeletal-associated protein (Arc) mRNA} and proteins {galactokinase 1 (GLK1) and brain-derived neurotrophic factor (BDNF)}.
<>Animals were randomly divided into 4 groups depending on the treatment given: stress (-)/H20, stress (-)/LvEO, stress (+)/H2O, and stress (+)/LvEO group. For behavioral testing, using an elevated plus-maze test, significant anxiolytic-like effects were seen in both the stress (-)/LVEO and stress (+)/LvEO groups, indicating that LvEO exerts anxiolytic-like effects regardless of the administration of water immersion stress. On expression analysis, the levels of NGFR and Arc mRNA were significantly lower in animals subjected to stress. Inhalation of LvEO, however, reversed this change, thus suggesting that LvEO negates the impact of stress on gene expression levels.
<>Meanwhile, significant decreases in expression levels were also observed in the stress (-)/LvEO group, which implies that LvEO, when given in a stress-free situation, may act as a stress stimulus. Taken together, our data suggest that inhalation of LvEO exerts bidirectional influences in the central nervous system (CNS) of animals, either attenuating the effects of stress or acting as a stressor, depending on the subject state."

Linalool has promising skin anti-aging properties by enhancing the collagen-producing protein TGF-b.

"<>Although previous studies have suggested that lavender oil promote wound healing, no study has examined the molecular mechanisms of its effect. In this study, we investigated the effect of lavender oil on various steps of wound healing and its molecular mechanism, focusing on transforming growth factor-β (TGF-β). Methods: Circular full-thickness skin wounds were produced on rats. Control solution or lavender oil was topically applied to the wounds on alternating days for 14 days. Results: The area of wounds topically treated with lavender oil was significantly decreased as compared to that of wounds of control rats at 4, 6, 8, and 10 days after wounding.

<>Topical application of lavender oil induced expression of type I and III collagen at 4 days after wounding, accompanied by an increased number of fibroblasts, which synthesize collagen. Induced expression of type III collagen by topical application of lavender oil was reduced to control level at 7 days after wounding although increased expression of type I collagen still continued even at 7 days, suggesting rapid collagen replacement from type III to type I in wounds treated with lavender oil.
<>Importantly, expression of TGF-β in wounds treated with lavender oil was significantly increased as compared to control. Moreover, an increased number of myofibroblasts was observed in wounds treated with lavender oil at 4 days after wounding, suggesting promotion of differentiation of fibroblasts through induction of TGF-β, which is needed for wound contraction."[518]

Aromatherapy Continued: Geraniol, Citronellol, a-Cedrene, & Limonene

These Volatile Organic Compounds are noteworthy, and recommended for oil diffuser use, but not topical nor oral application due to documented cytotoxicity.

[A] Limonene (Lemon oil) when inhaled for one hour per day is capable of reversing the neurological damage caused by an amyloid burden through increasing Acetylcholine in the brain alongside promoting bDNF expression. Limonene is prone to fast oxidation, making it better to not leave oils containing it in diffusers for longer than a few hours.

"<>The lemon essential oil (LEO), extracted from the fruit of lemon, has been used to treat multiple pathological diseases, such as diabetes, inflammation, cardiovascular diseases, depression and hepatobiliary dysfunction. The study was designed to study the effects of LEO on cognitive dysfunction induced by Alzheimer's disease (AD). We used APP/PS1 double transgene (APP/PS1) AD mice in the experiment; these mice exhibit significant deficits in synaptic density and hippocampal-dependent spatial related memory.
<>The effects of LEO on learning and memory were examined using the Morris Water Maze (MWM) test, Novel object recognition test, and correlative indicators, including a neurotransmitter (acetylcholinesterase, AChE), a nerve growth factor (brain-derived neurotrophic factor, BDNF), a postsynaptic marker (PSD95), and presynaptic markers (synapsin-1, and synaptophysin), in APP/PS1 mice. Histopathology was performed to estimate the effects of LEO on AD mice.
<>A significantly lowered brain AChE depression in APP/PS1 and wild-type C57BL/6L (WT) mice. PSD95/ Synaptophysin, the index of synaptic density, was noticeably improved in histopathologic changes. Hence, it can be summarized that memory-enhancing activity might be associated with a reduction in the AChE levels and is elevated by BDNF, PSD95, and synaptophysin through enhancing synaptic plasticity."[519]

[B] Geraniol (Rose oil) is a strong neuroprotectant against brain damage through antioxidant mechanisms.

"<>Geraniol (GE), an acyclic monoterpene, is a chief constituent of essential oils of herbs and fruits. It possesses diverse pharmacological actions like antioxidant, anti-inflammatory, anti-apoptotic, and anti-parkinson. However, its neuroprotective potential in stroke is yet to be explored at large. The present study evaluated the neuroprotective potential of GE against the global model of cerebral ischemia/reperfusion (I/R)-injury in rats.
<>Bilateral common carotid artery (BCCA) occlusion for 30 min followed by 7 days of reperfusion caused varied biochemical/enzymatic alterations viz. increase in levels of lipid peroxidation (LPO), nitric oxide (NO), xanthine oxidase (XO), and decrease in the levels of cerebroprotectives like superoxide dismutase (SOD), catalase (CAT), total thiols, and glutathione (GSH).
<>GE-pretreatment markedly reversed these changes and restored the levels of protective enzymatic and non-enzymatic antioxidants near to normal compared to I/R group. Besides, GE treatment showed marked improvement in anxiety-related behavior and neuronal deficits in animals subjected to I/R injury. Moreover, 2,3,5-triphenyl tetrazolium chloride (TTC)-stained rat brain coronal sections and histopathological studies revealed neuronal protection against I/R-injury, as evidenced by a reduction in infarct area (%) and an increase in hippocampal CA1 neuronal density in the GE-treated groups.
<>The results of this study revealed that GE exhibited potential neuroprotective activity by reducing oxidative stress and infarction area, and protecting hippocampal CA1 neurons against I/R-injury in the global stroke model in rats."[519.1]

[C] Citronellol (Rose oil) protects brain cells (dopaminergic cells) through promoting mTOR expression and through enhancing autophagy, and of course by way of antioxidant and anti-inflammatory mechanisms.

"<>Citronellol, a monoterpene found in the essential oils of Cymbopogo plants has been reported to possess various biological properties. In the present study, we investigated the neuroprotective mechanisms of citronellol against rotenone induced neurodegeneration by using rat model of Parkinson's disease (PD).
<>Our results demonstrated that oral administration of citronellol prevented rotenone induced reactive oxygen species production, lipid peroxidation and enhanced Nrf2 expression, catalase, glutathione peroxidase and superoxide dismutase levels in the brain. Enzyme-linked immunosorbent assays showed that citronellol reduced secretion of TNF-α, IL-1β, IL-6 and decreased MMP-9 expression levels. Further, citronellol prevented rotenone induced microglia (Iba-1 staining) and astrocyte (GFAP staining) activation. Western blot analysis showed that citronellol significantly decreased the expression of cyclooxygenase-2 and inducible nitric oxide synthase-2 that are key markers of neuroinflammation.

<>We further evaluated the effect of citronellol on dopaminergic neurons in substantia nigra pars compacta (SNpc) and striatum (ST) which are key anatomical structures in PD. Tyrosine hydroxylase (TH) immunoreactivity showed that citronellol preserved Tyrosine hydroxylase (TH) positive dopaminergic neurons and enhanced TH striatal expression levels significantly compared to rotenone alone group. Further, to understand the effect of citronellol on apoptosis and proteotoxicity, we evaluated apoptotic markers (Bax, Bcl-2), growth regulator (mTOR) and α-synuclein expression.
<>Citronellol attenuated rotenone induced expression of pro-apoptotic protein Bax, reduced α-synuclein expression and enhanced Bcl-2 and mTOR levels. In addition, citronellol modulated autophagy pathway by decreasing LC-3 (Microtubule-associated proteins) and p62 levels. Taken together, our results demonstrate that citronellol protected dopaminergic neurons through its antioxidant, anti-inflammatory, anti-apoptotic and autophagy modulating properties."[519.2]

[D] a-Cedrene (Cedarwood oil) is myogenic by way of enhancing CREB activity in skeletal muscle through activation of the Odorant Receptor MOR23. Just how much Cedarwood oil one would have to inhale to experience a statistically significant effect on muscle growth is, as expected, unknown currently. Cedarwood oil is highly cytotoxic and capable of damaging skin cells, therefore using it topically or orally is an unwise idea, but remember, most VOC's enter into systemic circulation through inhalation.

"<>Scope: Skeletal muscle atrophy is a common and debilitating condition that lacks an effective therapy. In this study, the effects of α-cedrene are tested, a natural ligand of mouse olfactory receptor 23 (MOR23) whose ectopic function regulating myogenesis on skeletal muscle growth was reported recently.
<>Methods and results: α-Cedrene not only stimulated hypertrophy but also attenuated free fatty acid-induced atrophy of cultured skeletal myotubes, as evidenced by an increased myotube diameter, fusion index, and total cellular protein content. These hypertrophic and antiatrophic properties of α-cedrene in cultured myotubes were confirmed in corresponding mouse models. The skeletal muscle mass, total muscle protein content, average cross-sectional area of myofibers, and muscle strength were significantly greater in α-cedrene-treated mice compared with untreated animals during either a regular chow diet or high-fat diet. Receptor knockdown experiments using RNA interference in cultured skeletal myotubes revealed that the hypertrophic and antiatrophic properties of α-cedrene may be mediated by MOR23. <>Furthermore, α-cedrene induced the expression of MOR23 and enhanced its downstream cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-cyclic AMP-responsive element-binding protein (CREB) signaling in the skeletal muscle of mice fed chow or high-fat diet.
<>Conclusions: α-Cedrene is a promising agent that may be applied to enhance the mass and strength of skeletal muscle."[519.3]

[D2] As an elaboration of the previous abstract, and quite strangely, our muscle tissue contains Odorant Receptors like MOR23, which associate with and are essential for efficient myogenesis to occur.

"<>Odorant receptors (ORs) in the olfactory epithelium bind to volatile small molecules leading to the perception of smell. ORs are expressed in many tissues but their functions are largely unknown. We show multiple ORs display distinct mRNA expression patterns during myogenesis in vitro and muscle regeneration in vivo. Mouse OR23 (MOR23) expression is induced during muscle regeneration when muscle cells are extensively fusing and plays a key role in regulating migration and adhesion of muscle cells in vitro, two processes common during tissue repair. A soluble ligand for MOR23 is secreted by muscle cells in vitro and muscle tissue in vivo. MOR23 is necessary for proper skeletal muscle regeneration as loss of MOR23 leads to increased myofiber branching, commonly associated with muscular dystrophy. Together these data identify a functional role for an OR outside of the nose and suggest a larger role for ORs during tissue repair."[519.4]

!?CAUTION?! Oral 1,8-Cineole !?CAUTION?!

On Toxicity, it is my *opinion*, and I may be severely wrong, that anything at or below 1/10th of a Teaspoon of Eucalyptus Globulus oil consumed orally once per day will not result in noticeable organ toxicity, if used temporarily. Although an effective amount of this VOC will enter into the brain and bloodstream by way of inhalation, or topical application, there is still interesting research on oral consumption.
If you do experiment with orally administered Cineole, you should start with Eucalyptus leaf tea first, after consulting with a licensed *Doctor*.

"<>Two adult Indian men who unintentionally consumed eucalyptus oil presented to the emergency room of our institution with seizures. In both patients, arterial blood gas analysis showed the presence of severe metabolic acidosis. Both the patients were managed in the intensive care unit and received standard supportive care. Metabolic acidosis was corrected with intravenous bicarbonate infusion. They were successfully discharged on the fourth day.
<>A 22-year-old Indian man presented to the ER of our institution in a drowsy state at about 9.45 a.m. The patient had been asymptomatic until that morning, when he had one episode of seizure. He was accompanied to the ER by another Indian man, a 26-year-old who was a close friend. Upon further probing of the patient's history, the friend of the patient revealed that on the same morning, the patient had taken eucalyptus oil, around **15 ml** supposedly for abdominal pain. He had bought it in bottle form, and the bottle had the markings of eucalyptus oil written on it but no information regarding precautions or side effects. When it was revealed to the accompanying friend that eucalyptus oil may have been the cause of the patient's seizure, he also admitted to have consumed the same

substance that morning for similar complaints. Soon the accompanying friend also had a bout of seizure while in the ER."[520]

[A] Oral Cineole reverses the brain damage associated with a stroke.

"<>Sprague-Dawley rats were divided into 4 groups: sham group, SAH group, SAH + vehicle group, and SAH + EUC group. SAH was induced by endovascular perforation. In SAH + EUC group, 100 mg/kg EUC was administrated intraperitoneally at 1 h before SAH and 30 min after SAH, respectively. Neurological deficits were examined by modified Neurological Severity Scores (mNSS). The brain edoema was evaluated by wet-dry method. Neuronal apoptosis was detected by Nissl staining. The expression of Bcl-2, cleaved caspase-3, phospho-NF-κB p65, ionised calcium-binding adapter molecule-1 (Iba-1), nuclear factor erythroid-2 (Nrf-2), and haem oxygenase 1 (HO-1) were measured by Western blot. Expression of pro-inflammatory cytokines was detected by qRT-PCR. Oxidative stress markers were also measured.
<>EUC markedly relieved brain edoema (from 81.22% to 78.33%) and neurological deficits [from 16.28 to 9.28 (24 h); from 12.50 to 7.58 (48 h)]. EUC reduced neuronal apoptosis, microglial activation, and oxidative stress. EUC increased the expression of HO-1 (1.15-fold), Nrf2 (1.34-fold) and Bcl-2 (1.17-fold) in the rats' brain tissue, and down-regulated the expressions of cleaved caspase-3 (41.09%), phospho-NF-κB p65 (14.38%) and pro-inflammatory cytokines [TNF-α (34.33%), IL-1β (50.40%) and IL-6 (59.13%)]."[521]

[B] Oral Cineole enhances CREB.

"<>Objectives: A previous in vitro study reported that the monoterpene oxide 1,8-cineole (cineole) attenuates neuronal caused by oxygen-glucose deprivation/reoxygenation in culture. However, to date, there is no in vivo evidence showing neuroprotective effects of cineole against stroke. This study aimed to investigate whether cineole attenuates cerebral ischaemic damage in rats.
<>Methods: A rat model of middle cerebral artery occlusion (MCAO) followed by 24 h reperfusion was applied. Male rats were treated with oral cineole (100 mg/kg) for 7 consecutive days, then subjected to MCAO surgery. Infarct volume, neurologic deficits, apoptosis and expression levels of all-spectrin breakdown products of 145 kDa (SBDP145), transient receptor potential canonical (subtype) 6 (TRPC6) and phosphorylated CREB (p-CREB) were measured in ischaemic brain tissues.
<>Key findings: Cineole treatment significantly reduced infarct volume, neurological dysfunction, neuronal apoptosis, SBDP145 formation and TRPC6 degradation and enhanced p-CREB expression in MCAO rats compared with vehicle treatment. These neuroprotective effects were markedly suppressed by pharmacological inhibition of MEK or CaMKIV signalling.
<>Conclusions: Our study provides in vivo evidence demonstrating that cineole pretreatment attenuates ischaemic stroke-induced brain damage, mainly through blocking

calpain-induced TRPC6 degradation and activating CREB via MEK/CREB and CaMKIV/CREB signalling pathways."[522]

[C] Oral Cineole protects organ cells from toxicity.

"<>The current study was conducted to investigate the protective properties of Eucalyptus globulus leaves methanolic extract (EGLME) against diclofenac sodium (DS) induced hepatorenal and testicular toxicity in male rats. A total of 40 rats were equally divided into 4 groups, Control, Diclofenac sodium (DS), EGLME and DS + EGLME groups, respectively. DS and EGLME were administered orally at dose rate 2.5 and 100 mg/kg BW, 4 times/week for 8 weeks, respectively. Administration of DS distorted hepatorenal functions manifested by alteration of serum levels of ALT, AST, total protein and albumin, creatinine and urea with changes of histological architectures. DS caused reproductive toxicity represented by minimized sperm count, individual sperm motility and viability; depleted concentration of reduced glutathione (GSH) in testicular tissue; and decreased testosterone level with alteration in testicular histological features. In contrast, co-treatment of DS intoxicated rats with EGLME protected rats against the adverse effects of DS revealing enhancing properties of EGLME on rats' liver, kidney and testes.
<>In conclusion, we demonstrated that EGLME had a potent protecting property against DS induced hepatic, renal and testicular toxicity in male rats, with special concern to testicular tissue via modulation of GSH as an oxidant marker."[523]

[D] Oral Cineole enhances White Blood Cell count & may enhance myogenesis (Carcass weight).

"<>The study was conducted to investigate the effects of different levels of eucalyptus powder (EP), virginiamycin and probiotic on performance, immunity, blood components and carcass traits of broiler chickens. A total of 250, 1-day-old male broiler chickens (Ross 308) were randomly allocated to five treatments with five replicates and 10 chicks each, as a completely randomized design. The dietary treatments consisted of: basal diet (BD), BD+0.25% EP, BD+0.5% EP, BD+0.01% of diet probiotic (Protexin), BD+0.02% of diet antibiotic (virginiamycin).
<>Dietary supplementation did not affect feed intake, BW gain (BWG) and feed conversion ratio (FCR) during starter and grower phases, but BWG and FCR were affected during the finisher and whole periods ($P<0.05$). The highest BWG and lowest FCR were obtained in birds fed with virginiamycin and 0.5% EP.
<>Dietary supplementation significantly increased the relative weight of carcass and breast ($P<0.05$). Treatments had no effect on relative weights of internal organs and small intestine except for bursa that increased by treatments. Relative length of jejunum also increased by treatments ($P<0.05$). Antibody production against sheep red blood cells did not changed in primary titer (day 35), but it significantly increased in secondary titer (day

42) by 0.5% EP. White blood cell counts were increased and cholesterol decreased by dietary supplementation ($P<0.05$).
<>In conclusion, the results of this study showed that 0.5% EP served as a useful replacement for antibiotic and would improve performance and immune response of broiler chickens."[524]

[C] Eucalyptol promotes **alveoli regeneration** following cigarette smoke exposure! Quite astounding information to wield, but complex to put into action. I have an idea, that it is possible to attain the benefits of Eucalyptol on lung alveoli regrowth, at home. Applying Eucalyptus Globulus oil to a diffuser or even under your nose will have minimal effects on a cigarette smokers' lungs, due to VOC's being unstable in open air, and being readily absorbed in the nasal passages far before reaching lung tissue. But if a steam sauna is used with EG oil added to the steam tank, it must be possible for some of the liberated Cineole to absorb into the lungs. Furthermore, a certain amount of Cineole naturally reaches the lunges during entrance in serum, therefore it does not hurt to experiment with topical, or inhalable Eucalyptus Globulus use if you are a smoker, vaper, or if you suffer from any form of lung dysfunction.

"<>Background: Eucalyptol is a monoterpenoid oil present in many plants, principally the Eucalyptus species, and has been reported to have anti-inflammatory and antioxidative effects.
<>Hypothesis/purpose: Since the potential effect of eucalyptol on mouse lung repair has not yet been studied, and considering that chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide, the aim of this study was to investigate eucalyptol treatment in emphysematous mice.
Study design: Male mice (C57BL/6) were divided into the following groups: control (sham-exposed), cigarette smoke (CS) (mice exposed to 12 cigarettes a day for 60 days), CS + 1 mg/ml (CS mice treated with 1 mg/ml eucalyptol for 60 days), and CS + 10 mg/ml (CS mice treated with 10 mg/ml eucalyptol for 60 days). Mice in the CS and control groups received vehicle for 60 days. Eucalyptol (or the vehicle) was administered via inhalation (15 min/daily). Mice were sacrificed 24 h after the completion of the 120-day experimental procedure.
<>Methods: Histology and additional lung morphometric analyses, including analysis of mean linear intercept (Lm) and volume density of alveolar septa (Vv[alveolar septa]) were performed. Biochemical analyses were also performed using colorimetric assays for myeloperoxidase (MPO), malondialdehyde (MDA), and superoxide dismutase (SOD) activity, in addition to using ELISA kits for the determination of inflammatory marker levels (tumor necrosis factor alpha [TNF-α], interleukin-1 beta [IL-1β], interleukin 6 [IL-6], keratinocyte chemoattractant [KC], and tumor growth factor beta 1 [TGF-β1]). Finally, we investigated protein levels by western blotting (nuclear factor (erythroid-derived 2)-like 2 [Nrf2], nuclear factor kappa B [NF-κB], matrix metalloproteinase 12

[MMP-12], tissue inhibitor of matrix metalloproteinase 1 [TIMP-1], neutrophil elastase [NE], and elastin).
<>Results: Eucalyptol promoted lung repair at the higher dose (10 mg/ml), with de novo formation of alveoli, when compared to the CS group. This result was confirmed with Lm and Vv[alveolar septa] morphometric analyses. Moreover, collagen deposit around the peribronchiolar area was reduced with eucalyptol treatment when compared to the CS group. Eucalyptol also reduced all inflammatory (MPO, TNF-α, IL-1β, IL-6, KC, and TGF-β1) and redox marker levels (MDA) when compared to the CS group (at least $p < 0.05$). In general, 10 mg/ml eucalyptol was more effective than 1 mg/ml and, at both doses, we observed an upregulation of SOD activity when compared to the CS group ($p < 0.001$). Eucalyptol upregulated elastin and TIMP-1 levels, and reduced neutrophil elastase (NE) levels, when compared to the CS group.
<>Conclusion: In summary, eucalyptol promoted lung repair in emphysematous mice and represents a potential therapeutic phytomedicine in the treatment of COPD."[524.1]

Music

Most understand that music choice has a large effect on our moods and memory, but I believe that the music we choose to listen to is more of a litmus test for the current brain wave & thought patterns we are experiencing, a diagnosis by melody, and the research has confirmed this belief. It is obvious that what is considered *classical* intelligence (highly numerate, high reading comprehension, behavioral stability etc.) associates with not necessarily a certain musical genre, but the childhood-adulthood learning of a complex musical instrument, which shows numerous benefits to the developing brain by way of enhanced bDNF expression. We should all practice an instrument.

[A] Music is reflective of current mood, more than an effector of mood.

"<>The claim that listening to extreme music causes anger, and expressions of anger such as aggression and delinquency have yet to be substantiated using controlled experimental methods. In this study, 39 extreme music listeners aged 18–34 years were subjected to an anger induction, followed by random assignment to 10 min of listening to extreme music from their own playlist, or 10 min silence (control). Measures of emotion included heart rate and subjective ratings on the Positive and Negative Affect Scale (PANAS).
<>Results showed that ratings of PANAS hostility, irritability, and stress increased during the anger induction, and decreased after the music or silence. Heart rate increased during the anger induction and was sustained (not increased) in the music condition, and decreased in the silence condition. PANAS active and inspired ratings increased during music listening, an effect that was not seen in controls. The findings indicate that extreme music did not make angry participants angrier; rather, it appeared to match their

physiological arousal and result in an increase in positive emotions. Listening to extreme music may represent a healthy way of processing anger for these listeners."[525]

[B] Classical music & self-selected music lowers cortisol levels. Is it possible that self-selected "heavy metal" is also capable of lowering cortisol? I am dubious.

"<>Listening to classical and self-selected relaxing music after exposure to a stressor should result in significant reductions in anxiety, anger, and sympathetic nervous system arousal, and increased relaxation compared to those who sit in silence or listen to heavy metal music. Fifty-six college students, 15 males and 41 females, were exposed to different types of music genres after experiencing a stressful test. Several 4 x 2 mixed design analyses of variance were conducted to determine the effects of music and silence conditions (heavy metal, classical, or self-selected music and silence) and time (pre-post music) on emotional state and physiological arousal. Results indicate listening to self-select or classical music, after exposure to a stressor, significantly reduces negative emotional states and physiological arousal compared to listening to heavy metal music or sitting in silence."[526]

[C] Listening to music slightly reduces memory formation.

"<>Background music has been increasingly affecting people's lives. The research on the influence of background music on working memory has become a hot topic in brain science. In this paper, an improved electroencephalography (EEG) experiment based on n-back paradigm was designed. Fifteen university students without musical training were randomly selected to participate in the experiment, and their behavioral data and the EEG data were collected synchronously in order to explore the influence of different types of background music on spatial positioning cognition working memory. The exact low-resolution brain tomography algorithm (eLORETA) was applied to localize the EEG sources and the cross-correlation method was used to construct the cortical brain function networks based on the EEG source signals. Then the characteristics of the networks under different conditions were analyzed and compared to study the effects of background music on people's working memory.
<>The results showed that the difference of peak periods after stimulated by different types of background music were mainly distributed in the signals of occipital lobe and temporal lobe ($P < 0.05$). The analysis results showed that the brain connectivity under the condition with background music were stronger than those under the condition without music. The connectivities in the right occipital and temporal lobes under the condition of rock music were significantly higher than those under the condition of classical music. The node degrees, the betweenness centrality and the clustering coefficients under the condition without music were lower than those under the condition with background music. The node degrees and clustering coefficients under the condition of classical music were lower than those under the condition of rock music. It indicates that music stimulation increases the brain activity and has an impact on the working memory, and the effect of rock music is more remarkable than that of classical music.

The behavioral data showed that the response accuracy in the state of no music, classical music and rock music were 86.09% ± 0.090%, 80.96% ± 0.960% and 79.36% ± 0.360%, respectively.
<>We conclude that background music has a negative impact on the working memory, for it takes up the cognitive resources and reduces the cognitive ability of spatial location."[527]

[D] Practicing a musical instrument enhances bDNF, which probably correlates to the complexity of said instrument.

"<>Background and objectives: The aim of the study was to investigate the influence of musical practice on brain plasticity. BDNF (brain-derived neurotrophic factor) is a neurotrophin involved in neuroplasticity and synaptic function.
<>Materials and methods: We recruited 48 healthy subjects of equal age and sex (21 musicians and 27 non-musicians). All subjects were administered the AQ (Autism-Spectrum Questionnaire) and plasma levels (PLs) of BDNF, oxytocin (OT), and vasopressin (VP) were measured in the blood sample of every participant.
<>Results: The difference between BDNF PLs in the two groups was found to be statistically significant ($t = -2.214$, $p = 0.03$). Furthermore, oxytocin (OT) PLs and musical practice were found to be independent positive predictors of BDNF PLs ($p < 0.04$). We also found a negative correlation between BDNF PLs and AD (attention to detail) sub-scale score of AQ throughout the whole sample. Assuming BDNF PLs to be a marker of synaptic plasticity, higher PLs could be associated with the activation of alternative neural pathways: a lower score in the "attention to detail" sub-scale could imply greater flexibility of higher cerebral functions among musicians."[528]

[E] Self-selected music (SSM) enhances muscle explosiveness. Most likely because the stimuli of our favorite music, especially tracks we associate with training, facilitates certain motor memory patterns.

"<>In a study conducted by Lim et al., the subjects completed three 10-km cycling time trials on an ergometer in a control condition, or music delivered from 0 to 5 km or music delivered from 5 to 10 km. The subjects reported no difference in RPE, interpreting all the trials as being equally difficult. As in our current study, the subjects reported no difference in the bench press RPE between conditions, which may have been so because of the extended length and intensity of the exercise. We found SSM to have a positive effect on squat jump TOV, RVD, and RFD. Our findings are similar to that of Eliakim et al. who used the Wingate Anaerobic Test to measure power of elite adolescent volleyball players. Their subjects were exposed to arousing predetermined music characterized by 140 b·min−1 for 10 minutes before performing the Wingate test, and they found increased peak anaerobic power in the first 5 seconds. Based on these results, it appears that motivating and or SSM may be beneficial during acute explosive, high-intensity exercise."[529]

Bonus Information

Video Games are "Visual Nootropics"

Video Games that require cognitive flexibility, e.g., Platformers(Super Mario)[1] and Puzzle Games[2] appear to promote increases in Grey Matter volume in the brain. I would suggest if you are a PC gamer, or if you have a child who enjoys PC video games, you should play or gift the game Islands of Insight, as it is an excellent open world online puzzle-adventure game. Similarly, there are the Talos Principle games, available on most major consoles, and sold as digital or physical copies. If you are technologically challenged, or just dislike video games, I am sure working on physical puzzles would have a similar effect on the brain.

[1] "<>Video gaming is a highly pervasive activity, providing a multitude of complex cognitive and motor demands. Gaming can be seen as an intense training of several skills. Associated cerebral structural plasticity induced has not been investigated so far. Comparing a control with a video gaming training group that was trained for 2 months for at least 30 min per day with a platformer game, we found significant gray matter (GM) increase in right hippocampal formation (HC), right dorsolateral prefrontal cortex (DLPFC) and bilateral cerebellum in the training group. The HC increase correlated with changes from egocentric to allocentric navigation strategy. GM increases in HC and DLPFC correlated with participants' desire for video gaming, evidence suggesting a predictive role of desire in volume change. Video game training augments GM in brain areas crucial for spatial navigation, strategic planning, working memory and motor performance going along with evidence for behavioral changes of navigation strategy. The presented video game training could therefore be used to counteract known risk factors for mental disease such as smaller hippocampus and prefrontal cortex volume in, for example, post-traumatic stress disorder, schizophrenia and neurodegenerative disease."[529.1]

[2] "<>Playing video games is a popular leisure activity among children and adults, and may therefore potentially influence brain structure. We have previously shown a positive association between probability of gray matter (GM) volume in the ventral striatum and frequent video gaming in adolescence. Here we set out to investigate structural correlates of video gaming in adulthood, as the effects observed in adolescents may reflect only a fraction of the potential neural long-term effects seen in adults. On magnetic resonance imaging (MRI) scans of 62 male adults, we computed voxel-based morphometry to explore the correlation of GM with the lifetime amount of video gaming (termed joystick years).
<>We found a significant positive association between GM in bilateral parahippocamal region (entorhinal cortex) and left occipital cortex/inferior parietal lobe and joystick years ($P<0.001$, corrected for multiple comparisons). An exploratory analysis showed that the entorhinal GM volume can be predicted by the video game genres played, such as logic/puzzle games and platform games contributing positively, and action-based role-

playing games contributing negatively. Furthermore, joystick years were positively correlated with hippocampus volume. The association of lifetime amount of video game playing with bilateral entorhinal cortex, hippocampal and occipital GM volume could reflect adaptive neural plasticity related to navigation and visual attention."[529.2]

N**ervonic Acid**

A fatty acid you have likely never heard of that associates with Myelination, which is especially important to the Central Nervous System.

"<>The use of biomarkers to predict who will develop schizophrenia (or other psychoses) is a key theme in current psychiatric research that has important implications for the development of early, or even prophylactic, treatment strategies. Here, we report that decreased levels of nervonic acid (NA), a monounsaturated omega-9 fatty acid important in the biosynthesis of myelin, correlate with prodromal symptoms, and predict conversion to psychosis in young people at high clinical risk for psychosis."[530]

Gluten

Gluten is a protein found in certain grains that is added to the majority of baked goods to provide texture, taste, and volume. Many people consider themselves Gluten intolerant, but this is likely to be a form of media-induced hypochondria, but this does not mean that Gluten is beneficial to our health, as you will soon learn.

[A] Dietary Gluten promotes intestinal Bacteroides growth.

"<>Although short-term feeding studies demonstrated effects of grains, fiber, and gluten on gut microbiome composition, the impact of habitual intake of these dietary factors is poorly understood. We examined whether habitual intakes of whole and refined grains, fiber, and gluten are associated with gut microbiota in a cross-sectional study.
<>This study included 779 participants from the multi-ethnic Food and Microbiome Longitudinal Investigation study. Bacterial 16SV4 rRNA gene from baseline stool was amplified and sequenced using Illumina MiSeq. Read clustering and taxonomic assignment was performed using QIIME2. Usual dietary intake was assessed by a 137-item food frequency questionnaire. Association of diet with gut microbiota was assessed with respect to overall composition and specific taxon abundances.
<>Whole grain intake was associated with overall composition, as measured by the Jensen-Shannon divergence (multivariable-adjusted P trend for quartiles = 0.03). The highest intake quartile was associated with higher abundance of Bacteroides plebeius, Faecalibacterium prausnitzii, Blautia producta, and Erysipelotrichaceae and lower abundance of Bacteroides uniformis. These bacteria also varied by dietary fiber intake. Higher refined grain and gluten intake was associated with lower Shannon diversity (P trend < 0.05).

<>These findings suggest that whole grain and dietary fiber are associated with overall gut microbiome structure, largely fiber-fermenting microbiota. Higher refined grain and gluten intakes may be associated with lower microbial diversity."[530.1]

[B] Wheat Gluten forms Amyloids during heat treatment. What this means for digestion, I do not know, but it can't be good in the long term.

"<>Amyloid fibrils have excellent structural characteristics, such as a high aspect ratio, excellent stiffness, and a wide availability of functional groups on the surface. More studies are now focusing on the formation of amyloid fibrils using food proteins. Protein fibrillation is now becoming recognized as a promising strategy for enhancing the function of food proteins and expanding their range of applications. <>Wheat gluten is rich in glutamine (Q), hydrophobic amino acids, and the α-helix structure with high β-sheet tendency. These characteristics make it very easy for wheat gluten to form amyloid fibrils. The conditions, formation mechanism, characterization methods, and application of amyloid fibrils formed by wheat gluten are summarized in this review. Further exploration of amyloid fibrils formed by wheat gluten will reveal how they can play a significant role in food, biology, and other fields, especially in medicine."[530.2]

Soy Products

[A] Soy Isoflavones inhibit myogenesis.

"<>Soy isoflavones display estrogenic activity in humans and animals, and thus are referred to as phytoestrogens. This study was performed to observe the effects of the soy isoflavones genistein, daidzein, and glycitein on cell cultures of rat skeletal muscles. [3H]Thymidine incorporation was used to determine cell proliferation, while protein synthesis and degradation were determined by tracking radiolabeled leucine. For the proliferation studies, insulin, estradiol, genistein, daidzein, or glycitein was supplemented at 0, 0.04, 0.08, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10, or 20 microM, respectively, or in combinations with final concentrations of 0, 0.1, 1, or 10 microM. Genistein reacted most similarly to estradiol, inhibiting proliferation at > or = 1 microM ($P < .001$).
<>A combination of phytoestrogens resulted in significant inhibition of cell proliferation, but not to the extent observed with genistein alone. For the protein synthesis and degradation experiments, treatments of 0.1 microM dexamethasone or 1 microM concentrations of insulin, genistein, daidzein, or glycitein were used. Phytoestrogens did not inhibit or stimulate protein degradation or synthesis ($P > .05$). A one-tailed univariate analysis of variance revealed a trend ($P < or = .1$) in protein stimulation with genistein and glycitein treatments.
<>These results suggest that the tyrosine kinase inhibiting activity of genistein may be affecting phosphorylation of the mitosis-promoting factor, preventing the advancement of the mitotic cell cycle. In addition, at higher total combined concentrations, daidzein and glycitein may be able to outcompete genistein for receptor sites. These results suggest

that soy isoflavones in the diet may potentially modulate normal growth and development in humans and animals that ingest soy-based products."[531]

[B] Isoflavones are neurotoxic to male brains.

"<>Adult male hooded Lister rats were either fed a diet containing 150 microg/g soya phytoestrogens or a soya-free diet for 18 days. This concentration of phytoestrogens should have been sufficient to occupy the oestrogen-beta, but not the oestrogen-alpha, receptors. Using in situ hybridisation, significant reductions were found in brain-derived neurotrophic factor (BDNF) mRNA expression in the CA3 and CA4 region of the hippocampus and in the cerebral cortex in the rats fed the diet containing phytoestrogens, compared with those on the soya-free diet. No changes in glutamic acid decarboxylase-67 or glial fibrillary acidic protein mRNA were found. This suggests a role for oestrogen-beta receptors in regulating BDNF mRNA expression."[532]

Fluoride

Fluoride is a very strange chemical that is used to "prevent tooth decay" by inclusion in toothpastes, and even many municipal tap waters. It is clearly a neurotoxin even in subacute concentrations, thus making the commonly parroted natural medicine practitioner talking point of "fluoride deactivating the pineal gland" a reality and not a conspiracy. Interestingly, the idea that fluoride could damage the pineal gland was originally posited not by a hippy, or madman, but by a British researcher named Jennier Luke in the 1990s.

It is frightening that many governments push for and continue to use fluoride in their tap water, with the excuse being "to prevent tooth decay", I suppose intellectual disability is a fair trade for sparkling teeth, right?

[A] Extended fluoride intake causes impairments to behavioral flexibility, and this is demonstrated by "dental fluorosis" or the appearance of white or yellow spots on the teeth, and potentially degradation of enamel. Yes, that's right, fluoride can cause the deterioration of teeth.

"<>Since clinical case reports suggest that sodium fluoride (NaF) intoxication may impair learning and memory, the objective of the present study was to evaluate the effects of NaF on two memory tasks: open-field habituation and two-way active avoidance. Adult male rats were exposed to NaF in drinking water at three concentrations for 30 days: 1.54 (control, tap water), 50 and 100 ppm NaF (corresponding to an intake of 0.10+/-0.005, 5.15+/-0.14, and 10.77+/-0.39 mg/kg of NaF, respectively).
<>At day 30, the rats were placed in an open-field and retested after 24 h (test session) to measure habituation. In the two-way active avoidance task, another three groups of rats were trained in a 30-trial training session and tested again 24 h later (test session). Dental fluorosis was also evaluated.

<>Habituation was impaired by 50 and 100 ppm, but not by 1.54 ppm NaF. Moreover, 100 ppm NaF reduced the number of avoidance responses in the active avoidance task. No locomotor impairment was observed. Mild dental fluorosis in rat incisor teeth was found in the 50 and 100 ppm NaF groups. Overall, these results suggest that moderate intoxication with sodium fluoride has potentially deleterious effects on learning and memory."[532.1]

[B] Fluoride causes long lasting alterations of brain neurotransmitter levels, similarly to antidepressants.

Memory impairment induced by sodium fluoride is associated with changes in brain monoamine levels that are not recovered after withdrawal.

"<>Previous studies suggest that sodium fluoride (NaF) can impair performance in some memory tasks, such as open-field habituation and two-way active avoidance. In the present study, we evaluated the effect of NaF intake (100 ppm in drinking water for 30 days) and its short-term (15 days) withdrawal on open-field habituation and brain monoamine level.
<>Adult male rats were allocated to three groups: tap water (NaF 1.54 ppm) for 45 days (control group); 15 days of tap water followed by NaF for 30 days; and NaF for 30 days followed by 15 days of tap water.
<>The results showed that NaF impairs open-field habituation and increases noradrenaline (NA) and serotonin (5-HT) in the striatum, hippocampus and neocortex. Dopamine (DA) increase was restricted to the striatum. Short-term NaF withdrawal did not reverse these NaF-induced changes, and both NaF treatments led to a mild fluorosis in rat incisors. No treatment effect was seen in body weight or fluid/water consumption.
<>These results indicate that sodium fluoride induces memory impairment that outlasts short-term NaF withdrawal (2 weeks) and may be associated with NA and 5-HT increases in discrete brain regions."[532.2]

[C] In an excellently well formulated open access study, Tetsuo Nakamoto1, & H Ralph Rawls discuss the developmental neurotoxicity of Fluoride, and its relation to decreased IQ scores, and other physiological derangements such as thyroid dysfunction and bone disease (omitted).

Fluoride and Intelligence quotient (IQ)

"<>Prenatal exposure to various substances that might not be toxic to adults but could cause neurobehavioral deficit in children. Therefore, the developing brain tends to be much more susceptible to nutritional stress than the adult brain. Some neurodevelopmental disorders are reported to be learning disabilities, sensory deficits, and developmental delays. Subclinical stages of these disorders might also be common. If the developmental process is inhibited, the consequences could be permanent.

<>In a 2006 study, fluoride is mentioned as a possible factor which might affect brain development, and further in-depth studies were suggested. Since then, fluoride has been identified as a developmental neurotoxicant.
Children who consumed water with higher levels of fluoride (water fluoride: 2.47±0.79 mg/L; range: 0.57–4.50 mg/L) reported significantly decreased IQ compared to that of children who consumed water with lower levels of fluoride (water fluoride: 0.36±0.15 mg/L; range: 0.18–0.76 mg/L) in China.
<>As the fluoride level in drinking water increased, the IQ fell and the rates of mental retardation and borderline intelligence increased. Furthermore, the children's IQ and their parents' education level and family income do not show any association.
<>These decreases of IQ from the higher contents of fluoride in the drinking water consumed during the growing period have also been reported in India, Iran and among the frequent tea-consuming children in Taiwan. Systematic reviews and meta-analyses have suggested the possibility of an adverse effect of high fluoride exposure on children's neurodevelopment."

Fluoride and thyroid gland

"<>A clear relationship between fluorosis and iodine deficiency disorders was recently shown for the first time. Because fluorosis is also prevalent in our society, these children have shown dental fluorosis symptoms that may need to be investigated in relation to thyroid stimulating hormone (TSH) and thyroid hormones, freeT4 and freeT3. It should also be noted that even in some of the children in the control group who consumed "safe" water (<1.0 ppm F–), fluoride levels in blood and urine were above current upper limits. This indicates fluoride ingestion, from foods and beverages and dental products such as toothpaste. In those children, disturbances in thyroid hormone ratios have been observed.
<>Hypothyroidism in the mother resulted in lowered IQ in the offspring. Hearing impairment in children ingesting high fluoride and living in endemic areas of iodine deficiency is reported 63. It has recently been reported that the serum fluoride concentration had a significant relationship with thyroid hormone (FT3/FT4) and TSH concentration among 8-to-15-year-old children."

Fluoride and pineal gland

"<>Tapp and Huxley examined calcium contents of various age group from pineal gland. They have found that significant amounts of calcium are present in the pineal glands of children. Further, the higher weights of female glands could be accounted for in part by their higher calcium content. The pineal gland is a mineralizing tissue and the calcified concretions are composed of hydroxylapatite (HA). It is likely that extremely high level of substitution in the crystal structure of pineal HA by fluoride. <>The Aged human pineal gland was found the positive correlation between fluoride content and calcium of the pineal gland. Apparently fluoride accumulates freely in the pineal gland, although the amount of fluoride present differs from one sample to others. Therefore, it is likely the

age independence of pineal calcification. The pineal gland produces melatonin, a hormone related to setting the rhythms and duration of sleep. The degree of calcification has been associated with a decreased secretion of melatonin. Thus, this could result in the disturbance of circadian rhythms and sleep patterns.

Fluoride and possible fetal origins of adult diseases

"<>Disease may originate in utero. Fetal nutrition plays an important role for newborns and affects health during child- and adulthood. It is well reported in epidemiological studies that undernourished babies will more likely develop various disease in later life. For example, low rates of growth before birth are linked to the development of coronary heart disease, stroke, diabetes, and hypertension in later life.
<>These associations are explained by a phenomenon known as programming. "Programming" occurs when an early stimulus or insult, operating at a critical or sensitive period, results in permanent or long-term changes in the structure or function of the organism. The lasting changes in structure and function are often caused by one of the nutritional stresses acting at critical periods of growth during the early developmental period."
↓ continued
"<>We do not know the mechanism of how fluoride leaves lasting imprints on the body and how it gives rise to possible diseases in later life. From the prenatal study with animals, it is apparent that fluoride will pass through utero-placental blood flow and has accumulated in the mandibular incisor and epiphysis during pregnancy."[532.3]

Vanadium

Vanadium destroys dopaminergic neurons.

"<>Environmental exposure to neurotoxic metals through various sources including exposure to welding fumes has been linked to an increased incidence of Parkinson's disease (PD). Welding fumes contain many different metals including vanadium typically present as particulates containing vanadium pentoxide (V_2O_5). However, possible neurotoxic effects of this metal oxide on dopaminergic neuronal cells are not well studied.
<>In the present study, we characterized vanadium-induced oxidative stress-dependent cellular events in cell culture models of PD. V_2O_5 was neurotoxic to dopaminergic neuronal cells including primary nigral dopaminergic neurons and the EC50 was determined to be 37 microM in N27 dopaminergic neuronal cell model. The neurotoxic effect was accompanied by a time-dependent uptake of vanadium and upregulation of metal transporter proteins Tf and DMT1 in N27 cells.

<>Additionally, vanadium resulted in a threefold increase in reactive oxygen species generation, followed by release of mitochondrial cytochrome c into cytoplasm and subsequent activation of caspase-9 (>fourfold) and caspase-3 (>ninefold). Interestingly, vanadium exposure induced proteolytic cleavage of native protein kinase Cdelta (PKCdelta, 72-74 kDa) to yield a 41 kDa catalytically active fragment resulting in a persistent increase in PKCdelta kinase activity. Co-treatment with pan-caspase inhibitor Z-VAD-FMK significantly blocked vanadium-induced PKCdelta proteolytic activation, indicating that caspases mediate PKCdelta cleavage. Also, co-treatment with Z-VAD-FMK almost completely inhibited V2O5-induced DNA fragmentation.
<>Furthermore, PKCdelta knockdown using siRNA protected N27 cells from V2O5-induced apoptotic cell death. Collectively, these results demonstrate that vanadium can exert neurotoxic effects in dopaminergic neuronal cells via caspase-3-dependent PKCdelta cleavage, suggesting that metal exposure may promote nigral dopaminergic degeneration."[533]

Curcumin is not a panacea

Turmeric and its resulting extract of chemical components, Curcumin (Curcuminoids), are not a good supplement to take, especially if you are an aged human being. Not only does Turmeric contain extremely high levels of oxalates, but Curcumin supplementation is associated with the increased growth of multiple species of toxic intestinal bacteria, which may explain why diabetes is so prevalent in India. Although curcuminoids have paradoxical antioxidant, myogenic, & neurogenic benefits, they do not have good bioavailability, making curcumin a supplement best used acutely, in high dosages, but never chronically (for extended periods of times) due to the risk of dysbiosis.

"<>Background: Curcuma longa (common name: turmeric) and one of its biologically active constituents, curcumin, have received increased clinical attention. Insufficient data exist on the effects of curcumin and turmeric on the gut microbiota and such studies in humans are lacking.
<>Methods: Turmeric tablets with extract of piperine (Bioperine) (n = 6), curcumin with Bioperine tablets (n = 5), or placebo tablets (n = 3) were provided to healthy human subjects and subsequent changes in the gut microbiota were determined by 16S rDNA sequencing.
<>Results: The number of taxa detected ranged from 172 to 325 bacterial species. The placebo group displayed an overall reduction in species by 15%, whereas turmeric-treated subjects displayed a modest 7% increase in observed species posttreatment. Subjects taking curcumin displayed an average increase of 69% in detected species. The gut microbiota response to treatment was highly personalized, thus leading to responders and nonresponders displaying response concordance. These "responsive" subjects defined a signature involving uniform increases in most Clostridium spp., Bacteroides spp., Citrobacter spp., Cronobacter spp., Enterobacter spp., Enterococcus spp., Klebsiella spp., Parabacteroides spp., and Pseudomonas spp. Common to these subjects was the reduced relative abundance of several Blautia spp. and most Ruminococcus spp.

<>Conclusions: All participants' microbiota displayed significant variation over time and individualized response to treatment. Among the responsive participants, both turmeric and curcumin altered the gut microbiota in a highly similar manner, suggesting that curcumin may drive the majority of observed changes observed in turmeric-treated subjects."[533.1]

Dietary Aluminum exposure

Aluminum Beverages contain high levels of absorbable and toxic Aluminum.

"<>Objective: To examine the possibility that aluminium beverage cans contribute to the dietary level of aluminium. Method: The aluminium content of a variety of beverages from aluminium cans and glass containers was measured. Results: The contents of 106 aluminium cans and bottles representing 52 different beverages all had a higher aluminium content than Newcastle tap water at 1.4 mumol/L, ranging as high as 385 mumol/L. Non-cola soft drinks averaged 33.4 mumol/L from cans and 5.6 mumol/L from bottles. Cola drinks averaged 24.4 mumol/L from cans and 8.9 mumol/L from bottles, whereas beer in cans or bottles averaged about 6 mumol/L. <>Conclusions: In general, the aluminium content of beverages from aluminium cans was higher than that from glass containers, and it rose with decreasing pH. Within a given category there was a wide variation in aluminium content. If the speculative link between aluminium intake and Alzheimer's disease is established then beverages from aluminium cans, particularly soft drinks, may be a risk factor.[534]

Oxalic Acid: A Potential Aging Accelerator?

Oxalate is present in high concentrations in certain foods, and even supplements such as Turmeric. They are reduced during cooking, especially steam cooking. It is a possibility that it not only accumulates in the kidneys, but also other parts of the body as we age, it might therefore be an intelligent decision to reference the freely available albeit somewhat contradictory oxalate food content reference papers on the internet, to restrict your dietary consumption of this ignored chemical.

[A] "<>Background: Although autistic spectrum disorders (ASD) are a strongly genetic condition certain metabolic disturbances may contribute to clinical features. Metabolism of oxalate in children with ASD has not yet been studied.
Aim: The objective was to determine oxalate levels in plasma and urine in autistic children in relation to other urinary parameters.
<>Method: In this cross-sectional study, plasma oxalate (using enzymatic method with oxalate oxidase) and spontaneous urinary calcium oxalate (CaOx) crystallization (based on the Bonn-Risk-Index, BRI) were determined in 36 children and adolescents with ASD

(26 boys, 10 girls) aged 2–18 years and compared with 60 healthy non-autistic children matched by age, gender and anthropometric traits.
Results: Children with ASD demonstrated 3-fold greater plasma oxalate levels [5.60 (5th–95th percentile: 3.47–7.51)] compared with reference [(1.84 (5th–95th percentile: 0.50–4.70) μmol/L ($p < 0.05$)] and 2.5-fold greater urinary oxalate concentrations ($p < 0.05$). No differences between the two groups were found in urinary pH, citraturia, calciuria or adjusted CaOx crystallization rates based on BRI. Despite significant hyperoxaluria no evidence of kidney stone disease or lithogenic risk was observed in these individuals.
<>Conclusions: Hyperoxalemia and hyperoxaluria may be involved in the pathogenesis of ASD in children. Whether this is a result of impaired renal excretion or an extensive intestinal absorption, or both, or whether Ox may cross the blood brain barrier and disturb CNS function in the autistic children remains unclear. This appears to be the first report of plasma and urinary oxalate in childhood autism."[534.1]

[B] Dietary oxalates promote a systemic pro-inflammatory response, which would be of useful application if not for the risk of brain crystal deposits.

"<>Several cytokines including IL-6, TNF-α, IL-1β, have been reported to be influenced by diet. To determine whether dietary oxalate loading could modify cytokine and chemokine levels in circulation, we measured plasma cytokines and chemokine levels using a multiplex immunoassay system. We previously reported that patients with CaOx kidney stones have elevated plasma IL-6 cytokine levels. Consistent with these findings, we determined that a dietary oxalate load significantly increased IL-6 levels in healthy adults. Furthermore, oxalate significantly reduced key anti-inflammatory cytokines (i.e., IL-10 and IL-13) and a chemokine (i.e., MCP-1) vital for monocyte recruitment. Oxalate also caused differential inflammatory signaling in the three different types of monocyte cellular bioenergetic responders. The decreased responders had a significant increase in IL-6 plasma levels which is consistent with our earlier data in CaOx stone formers. These same individuals also had decreased anti-inflammatory cytokine (i.e., IL-13, IL-10, and IL-4) levels. There was no change in IL-6 levels in the same or increased cohort. Further, we did not observe any correlation between plasma cytokines and chemokines with monocyte cellular bioenergetics. These data support the premise that a dietary oxalate load promotes pro-inflammatory responses and reduces anti-inflammatory responses and this could be occurring in the patient population."[534.2]

[C] Foods high in Oxalate. [534.3]

1/2cup Cooked Spinach 755mg
1/2cup Rhubarb 541mg
1-cup Rice Bran 281mg

1-cup Cooked Buckwheat Groats 133mg
1oz Almonds 122mg
1-cup Miso Soup 111mg
1-cup Cooked Wheat Berries 98mg
Medium Baked Potato with skin 97mg
1-cup Corn Grits 97mg
1-cup Soy Flour 94mg
1-cup Cooked Bulgar 86mg
1/2cup Beets 76mg
1/2cup Navy Beans 76mg
4tsp Cocoa Powder 67mg
1-cup Brown Rice Flour 65mg
1-cup Cornmeal 64mg
1-cup Cooked Millet 62mg
1/2cup Okra 57mg
4oz French Fries 51mg
1oz Cashews 49mg
1-cup Raspberries 48mg
1/2cup Yams 40mg
1-cup Walnuts 31mg
1/2cup Turnip 30mg
1cup Whole Grain Wheat Flour 29mg
1-Whole Orange 29mg
1-cup Sweet Potatoes 28mg
1oz Peanuts 27mg
1/2cup Pineapple 24-30mg
5-Pieces Dried Figs 24mg
1-cup Cooked Brown Rice 24mg
1/2cup Fava Beans 20mg
1-Date 19mg
1-Whole Avocado 19mg
10-Olives 18mg
1/2cup Tomato Sauce 17mg
1-cup All-Purpose Flour 17mg
1-Whole Kiwi 16mg
1/2cup Refried beans 16mg
1/2cup Parsnips 15mg
1/2cup Red Kidney Beans 15mg
1-cup Couscous 15mg

[C2] Spices / Condiments high in Oxalate. [534.4]

1tsp Sesame Seeds 114mg
1tsp Lemon Myrtle 49mg
1tsp Turmeric 46mg
1tsp Poppy Seeds 45mg
1tsp Ground Cloves 42mg
1tsp Celery Seeds 32mg
1tsp Ground Cinnamond 25mg
1tsp Cumin Seed 23mg
1tsp Fennel Seed 23mg
1tsp Allspice 20mg
1tsp Anise 20mg.

[C3] Beverages high in Oxalate. [534.5]

1-cup Star Fruit Juice 1990mg
1-cup Rhubarb Juice 496mg
1-cup Beetroot Juice 164mg
1-cup Mango Juice 27mg
1-cup Black Tea 27mg
1-cup Carrot Juice 23mg
1-cup Green Tea 21mg
1-cup Coconut Water 17mg

Canola oil

Rapeseed oil, now referred to as "Canola oil", contains a fatty acid that is toxic to cells called Erucic Acid, in [1] we see it has been known to cause myocardial lesions (especially in male mice) due to lipid accumulation, and in [2] we see that a diet rich in Canola oil accelerates amyloid deposition in mice prone to developing Alzheimer's Disease-like neuropathology.

[1] "<>Fully refined rapeseed oils containing different amounts of erucic acid (1.6%, 4.3% and 22.3%) were fed, at 20% by weight of diet, to weanling male and female Sprague-Dawley rats for periods up to 112 days. Transient myocardial lipidosis characterized by accumulation of fat droplets in myocardial fibers was marked in male and female rats fed oxidized and unoxidized rapeseed oil containing 22.3% erucic acid, moderate with rapeseed oil containing 4.3% erucic acid and very slight in rats fed rapeseed oil containing 1.6% erucic acid.
<>Peak intensity of myocardial lipidosis occurred at three to seven days and regressed thereafter. Focal myocardial necrosis and fibrosis occurred in male rats fed rapeseed oils containing different levels of erucic acid for 112 days. The incidence of myocardial

necrosis and fibrosis was markedly lower in female rats, and the incidence of these lesions in either sex was not affected by the state of oxidation of these oils.
<>In a second experiment, male rats were fed diets containing crude, partially refined or fully refined rapeseed oils. There was no correlation between the number of foci of myocardial necrosis and fibrosis and the state of refinement of the oils, but there were generally fewer lesions in rats fed those oils having the lowest levels of erucic acid."[535]

[2] "<>In recent years consumption of canola oil has increased due to lower cost compared with olive oil and the perception that it shares its health benefits. However, no data are available on the effect of canola oil intake on Alzheimer's disease (AD) pathogenesis. Herein, we investigated the effect of chronic daily consumption of canola oil on the phenotype of a mouse model of AD that develops both plaques and tangles (3xTg). To this end mice received either regular chow or a chow diet supplemented with canola oil for 6 months.
<>At this time point we found that chronic exposure to the canola-rich diet resulted in a significant increase in body weight and impairments in their working memory together with decrease levels of post-synaptic density protein-95, a marker of synaptic integrity, and an increase in the ratio of insoluble Aβ 42/40. No significant changes were observed in tau phosphorylation and neuroinflammation. <>Taken together, our findings do not support a beneficial effect of chronic canola oil consumption on two important aspects of AD pathophysiology which includes memory impairments as well as synaptic integrity. While more studies are needed, our data do not justify the current trend aimed at replacing olive oil with canola oil."[535.1]

Generic Psychotropic Medications are insidiously unreliable

Brand name medications may be expensive, but they are purified and possess well documented research regarding their pharmacodynamics. Generic medications unfortunately are often lower in potency than advertised, and they usually contain excess amounts of filler ingredients that are clearly designed to reduce gastrointestinal absorption such as "Lactose", "Talc", "Magnesium Stearate", "Silicon Dioxide", & "Microcrystalline cellulose".
Remember, you can ask for different generic suppliers to be ordered at a pharmacy so always avoid using pharmaceuticals that are noticeably *bloated* (larger than normal), such as with tablets or capsules, as this means there are too many filler ingredients.

"<>Background: Generic antidepressants are approved on the market based on evidence of bioequivalence to their brand-name versions. We aimed to assess whether generic antidepressants exert equal effectiveness as their brand-name counterparts for treating patients with depressive disorders.

<>Methods: In a nationwide, population-based cohort in Taiwan from 1997 through 2013, patients with a diagnosis of a depressive disorder aged between 18 and 65 years who were new users of antidepressant drugs were classified into either the brand-name group or the generic group. All patients were followed up until medication discontinuation or the end of the study period. We assessed the risk for hospitalization as a primary outcome and augmentation therapy, daily dose, medication discontinuation, or switching to another antidepressant as secondary outcomes.
<>Result: A total of 277 651 brand-name users (35.8% male; mean age: 41.2 years) and 270 583 generic users (35.8% male; mean age: 41.0 years) were divided into 10 different antidepressant groups (fluoxetine, sertraline, paroxetine, escitalopram, citalopram, venlafaxine, mirtazapine, moclobemide, imipramine, and bupropion). We found that patients treated with the generic form of sertraline, paroxetine, escitalopram, venlafaxine, mirtazapine, and bupropion demonstrated significantly higher risks of psychiatric hospitalization (adjusted hazard ratios ranged from 1.20–2.34), compared to their brand-name counterparts. The differences between brand-name antidepressants and their generic counterparts in secondary outcomes varied across different drugs."[535.2]

N.E.C.T.A.R.: Narcotics Enforcement Crew Tracking And Restricting

I feel it my duty to share this study, considering we have previously discussed the intelligence of bees, and because life is strange and humorous at times.
(Acronym coined by Meta AI)

"<>Illegal drugs exacerbate global social challenges such as substance addiction, mental health issues and violent crime. Police and customs officials often rely on specially-trained sniffer dogs, which act as sensitive biological detectors to find concealed illegal drugs. However, the dog "alert" is no longer sufficient evidence to allow a search without a warrant or additional probable cause because cannabis has been legalized in two US states and is decriminalized in many others. Retraining dogs to recognize a narrower spectrum of drugs is difficult and training new dogs is time consuming, yet there are no analytical devices with the portability and sensitivity necessary to detect substance-specific chemical signatures. This means there is currently no substitute for sniffer dogs.
<>Here we describe an insect screening procedure showing that the western honeybee (Apis mellifera) can sense volatiles associated with pure samples of heroin and cocaine. We developed a portable electroantennographic device for the on-site measurement of volatile perception by these insects and found a positive correlation between honeybee antennal responses and the concentration of specific drugs in test samples. Furthermore, we tested the ability of honeybees to learn the scent of heroin and trained them to show a reliable behavioral response in the presence of a highly-diluted scent of pure heroin.
<>Trained honeybees could therefore be used to complement or replace the role of sniffer dogs as part of an automated drug detection system. Insects are highly sensitive to

volatile compounds and provide an untapped resource for the development of biosensors. Automated conditioning as presented in this study could be developed as a platform for the practical detection of illicit drugs using insect-based sensors."[535.3]

Low EMF Sauna's inhibit angiogenesis

"<>The formation of new blood vessels is an essential therapeutic target in many diseases such as cancer, ischemic diseases, and chronic inflammation. In this regard, extremely low-frequency (ELF) electromagnetic fields (EMFs) seem able to inhibit vessel growth when used in a specific window of amplitude. To investigate the mechanism of anti-angiogenic action of ELF-EMFs we tested the effect of a sinusoidal magnetic field (MF) of 2 mT intensity and frequency of 50 Hz on endothelial cell models HUVEC and MS-1 measuring cell status and proliferation, motility and tubule formation ability. MS-1 cells when injected in mice determined a rapid tumor-like growth that was significantly reduced in mice inoculated with MF-exposed cells. In particular, histological analysis of tumors derived from mice inoculated with MF-exposed MS-1 cells indicated a reduction of hemangioma size, of blood-filled spaces, and in hemorrhage. In parallel, in vitro proliferation of MS-1 treated with MF was significantly inhibited.
<>We also found that the MF-exposure down-regulated the process of proliferation, migration and formation of tubule-like structures in HUVECs. Using western blotting and immunofluorescence analysis, we collected data about the possible influence of MF on the signalling pathway activated by the vascular endothelial growth factor (VEGF). In particular, MF exposure significantly reduced the expression and activation levels of VEGFR2, suggesting a direct or indirect influence of MF on VEGF receptors placed on cellular membrane.
<>In conclusion MF reduced, in vitro and in vivo, the ability of endothelial cells to form new vessels, most probably affecting VEGF signal transduction pathway that was less responsive to activation. These findings could not only explain the mechanism of anti-angiogenic action exerted by MFs, but also promote the possible development of new therapeutic applications for treatment of those diseases where excessive angiogenesis is involved."[536]

Hyperuricemia Intelligentsia

As it turns out, serum Uric Acid is associated with mental performance, as it has been shown individuals who suffer from gout have a higher intelligence[A-A2]. It may be a good idea to increase your dietary intake of Purines, those being Adenine, Guanine, and Xanthine, all precursor molecules of Uric Acid, to facilitate cognition and muscle performance through reducing certain free radicals. A high content of purines can be found in the foods and supplements listed in [B].

[A] "<>Gout is one of the rare diseases that defines its sufferers by class and culture. It is also one of the first chronic diseases to be clinically described. The Egyptians had

identified gout as a distinct disorder by 2640 bce. This paper traces the history of gout from its earliest recorded period down to modern times, with a particular emphasis on the cultural, political, geopolitical, and social aspects. Included is a discussion of its role in the American Revolution.
<>Today, gout is a well-understood clinically managed arthritic disease that excites little comment. This is an entirely modern perspective. For most of human history, gout was a disease of distinction that dominated much of medicine, playing the same role in Rome's third century bce aristocracy it would later play in the aristocracies of 17th and 18th century France and England, when each of these countries dominated the world. Because it was considered a disease of lifestyle until modern times, when genetics began to be understood, gout was associated with rich, high status Caucasian men and their excessive consumption of drink and rich foods.
<>It was virtually unknown in Asia, until Western dietary practices became widespread there. From earliest history, gout has been linked with high IQ and sexual promiscuity, which made it grist for artists and writers, and their social commentary up to the time of Dickens; this is discussed, with examples. Because of its association with the rich, gout also developed a powerful moralistic aspect, particularly during the Christian era when the concept of sin was a cultural fundamental. The loose living and indulgence of the rich and the gout it produced made the disease a parable of Christian ethics. The Italian poet Francesco Petrarch (1304-1374) was one of the first to establish this nuance, and it influenced how gout was seen for centuries. Part of what gave gout its special character was that while it tortured, it rarely killed.
<>Indeed, when death was a frequent visitor to families, it was thought a painful but welcomed prophylactic against diseases that did kill. Even in modern times, gout still favors the rich and powerful. American research conducted in the 1960s found that corporate executives, just like their English gentry, or Roman senatorial predecessors, had higher urate concentrations than their blue-collar employees."[536.1]

[A2] "<>Among mammals, there is a positive correlation between serum uric acid (UA) levels and life span. Humans have high levels of UA because they lack a functional urate oxidase (UOX) enzyme that is present in shorter lived mammals. Here, we show that male and female mice with UOX haploinsufficiency exhibit an age-related elevation of UA levels, and that the life span of female but not male UOX+/− mice is significantly increased compared to wild-type mice.
<>Serum UA levels are elevated in response to treadmill exercise in UOX+/− mice, but not wild-type mice, and the endurance of the UOX+/− mice is significantly greater than wild-type mice. UOX+/− mice exhibit elevated levels of brain-derived neurotrophic factor, reduced brain damage and improved functional outcome in a model of focal ischemic stroke. Levels of oxidative protein nitration and lipid peroxidation are reduced in muscle and brain tissues of UOX+/− mice under conditions of metabolic and oxidative

stress (running in the case of muscle and ischemia in the case of the brain), consistent with prior evidence that UA can scavenge peroxynitrite and hydroxyl radical.
<>Our findings reveal roles for UA in life span determination, endurance and adaptive responses to brain injury, and suggest novel approaches for protecting cells against injury and for optimizing physical performance."[536.1A]

[B] Sample Food Purine Content List: Full List @ [536.1B]

Meat: Dried Anchovies, Flounder, Lobster, Mackerel, Octopus, Oysters, Salmon, Sardines, Tuna, Chicken Breast,

Plants: Lentils, White Beans, Lima Beans, Miso Soup, Split Peas, Natto, Broccoli Sprouts, Maitake Mushroom, Shiitake Mushroom, Parsley, Wakame Seaweed.

Other: Brewer's Yeast (Super High), Chlorella (Super High), Spirulina (Very High), Royal Jelly (High).

Strangely, the USDA has made the excellent research paper on food purine content I reference here and of which I referenced years ago in my first book draft forbidden, but luckily we have Wayback Machine, I do suggest you download the webpage snapshot in case it to disappears.

The Gut Microbiome & Aberrant Neurodevelopment

A study by Great Plains Laboratory has proven many psychiatric illnesses such as Autism are related to intestinal Clostridium content, which leads to an excess of neurological Dopamine and abnormal behaviors (Autism).

"<>Many physicians treating children with autism have noted that the severity of autistic symptoms is related to the concentration of the *Clostridia* marker 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA) in urine. These are probably the children with autism with severe and even psychotic behavior treated with Risperdal and other anti-psychotic drugs, which block the activation of dopamine receptors by excess dopamine. I have identified a number of species of *Clostridia* species that produce HPHPA including *C. sporogenes*, *C.botulinum*, *C. caloritolerans*, *C. mangenoti*, *C. ghoni*, *C.bifermentans*, *C. difficile*, and *C. sordellii*. All species of *Clostridia* are spore formers and thus may persist for long periods of time in the gastrointestinal tracts even after antibiotic treatment with oral vancomycin and metronidazole.
<>How do the changes in brain neurotransmitters caused by *Clostridia* metabolites alter behavior? The increase in phenolic *Clostridia* metabolites common in autism significantly decreases brain dopamine beta hydroxylase activity. This leads to overproduction of brain dopamine and reduced concentrations of brain norepinephrine,

and can cause obsessive, compulsive, stereotypical behaviors associated with brain dopamine excess and reduced exploratory behavior and learning in novel environments that are associated with brain norepinephrine deficiency. Such increases in dopamine in autism have been verified by finding marked increases in the major dopamine metabolite homovanillic acid (HVA) in urine. The increased concentrations of HVA in urine samples of children with autism are directly related to the degree of abnormal behavior.

The concentrations of HVA in the urine of some children with autism are markedly abnormal."[536.2]

Deceitful Seasonings

On the Ketogenic Diet avoid all seasonings containing cornstarch or sugar, read the ingredients list on your kitchen seasonings! Do not consume Table Salt with "Yellow Prussiate of Soda" that is a code word for *Sodium Cyanide*.

In summary we have learned:

1. Efficient early wound healing (myogenesis) requires inflammation,
2. Chronic inflammation exacerbates aging,
3. Chronic inflammation is the cause of most forms of neurodegeneration,
4. Moderate Inflammation is important for physical growth & performance,
5. Moderate Inflammation delays aging,
6. Moderate Inflammation promotes cognitive memory,
7. Antioxidants suppress inflammation,
8. Antioxidants protect brain & muscle cells from atrophy and fibrosis,
9. Antioxidants promote myogenesis & neurogenesis,
10. Antioxidants delay certain forms of aging.

I do believe we can create a balance of inflammation, but you will never reach your absolute physical or mental potential through underdosing supplements or inhibiting exercise-induced angiogenesis. It is true that excess inflammation is the leading cause of physical & mental illness (including death), yet it is also true that angiogenesis is essential for neurological, cardiovascular, & muscular health. Therefore, I have written and *meticulously collected* the information in this book to argue in favor of my ideal modes of existence & hypothesis:

Inflammation Cycling

>>>>>>>>>>>>>>>>>>>>>>>FINAL WARNINGS<<<<<<<<<<<<<<<<<<<<<<<

As prophylaxis, remember, many chemicals will accumulate over months and years in your bloodstream and exert cytotoxic effects, even phytochemicals & vitamins, therefore you must **Cycle** between them.

A warning on **Blood Flow Restricted Training**; Remember there is a risk of cardiovascular events, and possibly as of yet unresearched musculotendon or nerve injuries. Do not engage in any form of B.F.R. / Occlusion Training, including my Incremental Occlusion Training without first consulting with a certified medical practitioner and receiving their explicit *approval*.

A warning on **TALMs**: Before you begin applying strange and potent Essential oils to your skin, ensure that the main chemical components of the oils are not cytotoxic to healthy cells in low concentrations, and always experiment with new TALMs by using lower amounts of Essential oil(s) to Carrier oil in the beginning, to test for allergies or other adverse skin reactions.

A warning on **Gastrointestinal Irritants**: Do not combine sugar alcohols, MCT oil, capsaicin, or lactose with supplements unless you intend on excreting them without absorption. Plan your supplement timing carefully.

A warning on engaging in **Inflammation Cycling** without cycling exercise intensity: If you choose to use antioxidants with strong anti-inflammatory effects while simultaneously training with high intensities (i.e. high loads, extreme tempos), you will undoubtedly overtrain your muscles, resulting in fast-to-slow twitch muscle fiber type conversion, or blunted hypertrophy.

A warning on extended **Pro-Inflammation Cycling**: Before and during a Pro-Inflammation Cycle, if you are of an older age, or on illicit drugs, it is of the utmost importance you get routine bloodwork, to ensure you are not at risk, or increasing your risk, of heart attacks, autoimmunity, or any other potentially fatal health event or condition. Also, do not neglect your Steady-state cardio, or you will expedite your inevitable death.

A warning on **IMC Workout Protocols**: Never continue following a strict workout protocol that demands higher intensity or higher load lifting if you begin to develop injuries, and if you have a preexisting injury, consider changing the protocol to suit your needs, such as increasing rest days between workouts, or decreasing loads lifted / exercise intensity. Do not train past injuries.

“For all practical purposes in judging human character, a man's actions and conscious expressions of thought are in most cases sufficient. Actions, above all, deserve to be placed in the front rank; for many impulses which penetrate into consciousness are neutralized by real forces in the psychic life before they find issue in action; indeed, the reason why they frequently do not encounter any psychic obstacle on their path is because the unconscious is certain of their meeting with resistances later.”

The Interpretation of Dreams: Chapter 10: Sigmund Freud

“The overflowing productivity of their minds has led one of my friends to assert that hysterics are the flower of mankind, as sterile, but as beautiful as double flowers.”

Josef Breuer: Preliminary Communication (On Hysterical Individuals)

“Life has always seemed to me like a plant that lives on its rhizome. Its true life is invisible, hidden in the rhizome. The part that appears above ground lasts only a single summer. Then it withers away—an ephemeral apparition. When we think of the unending growth and decay of life and civilizations, we cannot escape the impression of absolute nullity. Yet I have never lost a sense of something that lives and endures underneath the eternal flux. What we see is the blossom, which passes. The rhizome remains.”

Memories, Dreams, Reflection: Preface: Carl Jung

“Science and truth may be deemed to be like good, but not the good; the good has a place of honor yet higher.”

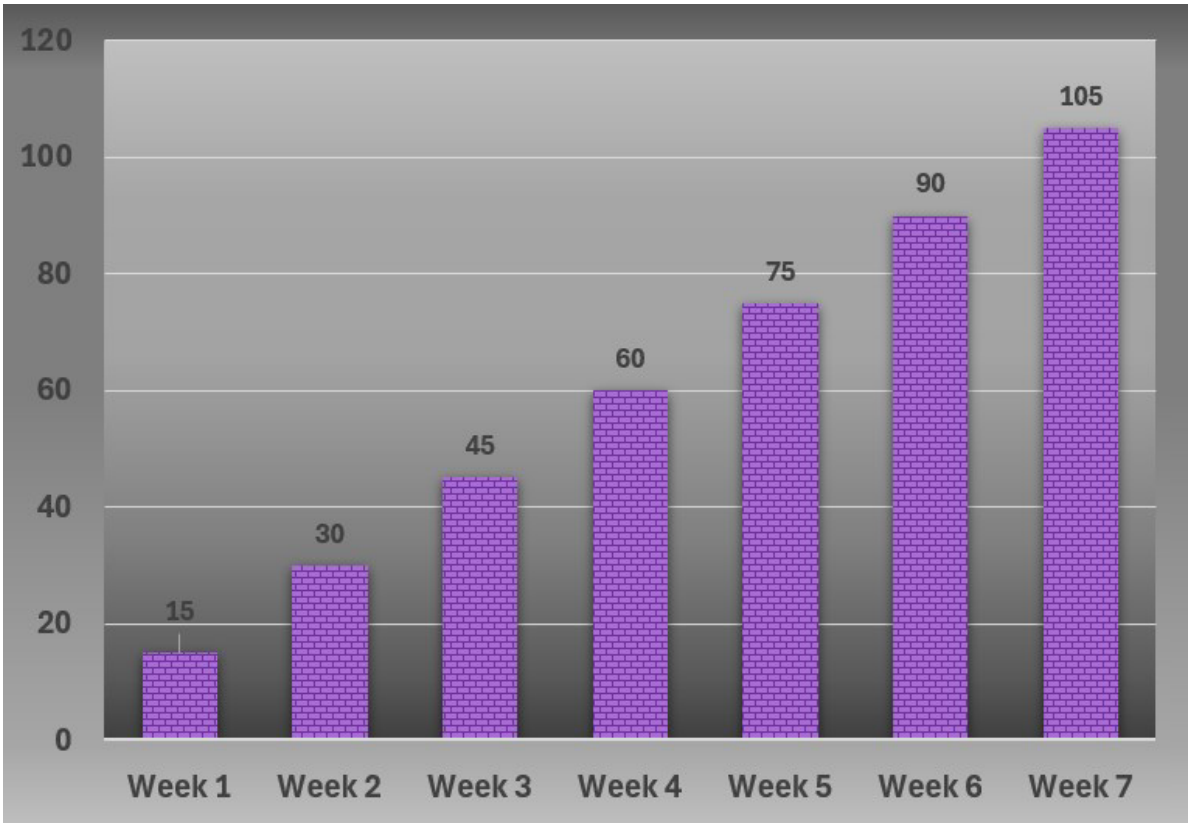
The Republic: Book 6 509 (508?) e: Plato

"Self-awareness is the most productive form of self-harm."

DS

IMC WORKOUT PROTOCOLS

15% Periodization Power Protocol © (15P)



Protocol Background: This routine took me around ten hours to formulate, although it seems extremely simple, I assure you it is not. Every working set is accounted for, making this an ideal resistance training protocol for growing muscle safely and effectively, it is mathematical perfection.

Protocol Guide: I suggest only utilizing one compound movement per muscle group, and one grip or stance width per cycle. To reiterate; Do not change your exercise or exercise variation (i.e., grip orientation, grip width, stance width, or range of motion) until the periodization is complete.

Each set is one single repetition, never more. If you fail a percentage increase either due to the inability to lift the weight slowly, or any other reason, start again in week one. Never add exercises, sets, or reps to a workout aside from a long aerobic / lactic acid training warmup. If you find asymmetry in your exercise form, such as an uneven bar path in the bench press, you can always change from a specialization in one heavy compound movement to one heavy isolation movement.

Every workout will total SEVEN sets, but they will differ in weight jumps AKA reach sets (pyramid sets), always following 15% incremental increases.
This protocol is strictly made for ET:SS [See: Extreme Tempo Superslow Training], with each repetition moving at a slow enough speed on the eccentric *and* concentric phase to appear buttery smooth and not jittery i.e., perfect motor pathway control. If you are unable to control a load throughout the entire range of motion of a selected exercise, and your muscles are jittery or shaking, you're either, A. Ego lifting, B. Using improper form, C. Overtrained / Injured, or D. Deficient in Electrolytes.

ARCS: Perform 60 Minutes at 60% Maximum Heart Rate Steady-State Cardio five-six days a week, ideally not on the same days as resistance training (always different muscle groups!).

Protocol Elaboration: By performing only singles you learn self-control and prevent overtraining. 15% increments are a perfect system to hypothetically achieve a 5% increase every seven weeks in your one rep maximum, that is, if you are healthy and achieve adequate recovery between workouts.

It is suggested that you follow ARCS (For Definition See: Specialization, Cardio, Injuries, & Antagonist Muscle Activation) to accelerate resistance-trained skeletal muscle regeneration further, but you may train all major muscle groups with this protocol and neglect cardio if you wish to shorten your lifespan. I have elaborated on the exact set layouts for those of you who will be confused by my math.

Because high load Superslow resistance training, whether eccentric or concentric, results in the greatest amount of musculoskeletal damage, do not attempt to train a muscle group more than once a week on this protocol with loads surpassing 15% your Regular-speed 1RM, or face the repercussions of injury. The set scheme is displayed in square brackets. Stretching should not be performed to prevent injury.

If you are focused solely on power and not myogenesis, you can perform a full pyramid of 15P, by descending the weeks when you reach a fail point, such as your 90% 1RM week, the following week would be 75%, until your reach 15% and then you would start the protocol over. Pyramid periodization is not the best option to grow muscle tissue as you will be nearly doubling the number of weeks you are lifting high loads.

Five days after your 15P workout, you should engage in a *very low load* (1-5% 1RM) Aerobic or Occlusion Training workout to promote angiogenesis and prevent vascular deconditioning. As for Occlusion Training, 50-Seconds x 5-Sets is suggested to be performed with the *exact same* specialized exercise and form, for power is dependent on technique. It is vital that this "light day" is composed of a load that you would consider laughable, as you must ensure your musculoskeletal system is prepared for the next tempo workout.

Most Importantly, this protocol, and many others I have formulated often breach the

guidelines detailed in my Recovery Periods Section, they are for temporary use only, to accrue maximal increases in muscle performance in short periods of time.

- WEEK 1: 15% 1RM SINGLE / 7-WORKING SETS, 1-SET TO REACH 15%. [SET 1-2-3-4-5-6-7: 15% SINGLE]

- WEEK 2: 30% 1RM SINGLE / 6-WORKING SETS, 2-SETS TO REACH 30%. [SET 1: 15% SINGLE, SET 2-3-4-5-6-7: 30% SINGLE]

- WEEK 3: 45% 1RM SINGLE / 5-WORKING SETS, 3-SETS TO REACH 45%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3-4-5-6-7: 45% SINGLE]

- WEEK 4: 60% 1RM SINGLES / 4-WORKING SETS, 4-SETS TO REACH 60%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3: 45% SINGLE, SET 4-5-6-7: 60% SINGLE]

- WEEK 5: 75% 1RM SINGLE / 3-WORKING SETS, 5-SETS TO REACH 75%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3: 45% SINGLE, SET 4: 60% SINGLE, SET 5-6-7: 75% SINGLE]

- WEEK 6: 90% 1RM SINGLE / 2-WORKING SETS, 6-SETS TO REACH 90%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3: 45% SINGLE, SET 4: 60% SINGLE, SET 5: 75% SINGLE, SET 6-7: 90% SINGLE]

- WEEK 7: 105% 1RM SINGLE / 1-WORKING SET, 7-SETS TO REACH 105%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3: 45% SINGLE, SET 4: 60% SINGLE, SET 5: 75% SINGLE, SET 6: 90% SINGLE, SET 7: 105% SINGLE]

- WEEK 8: 2X / WEEK RESISTANCE AEROBICS OR OCCLUSION TRAINING ONLY.

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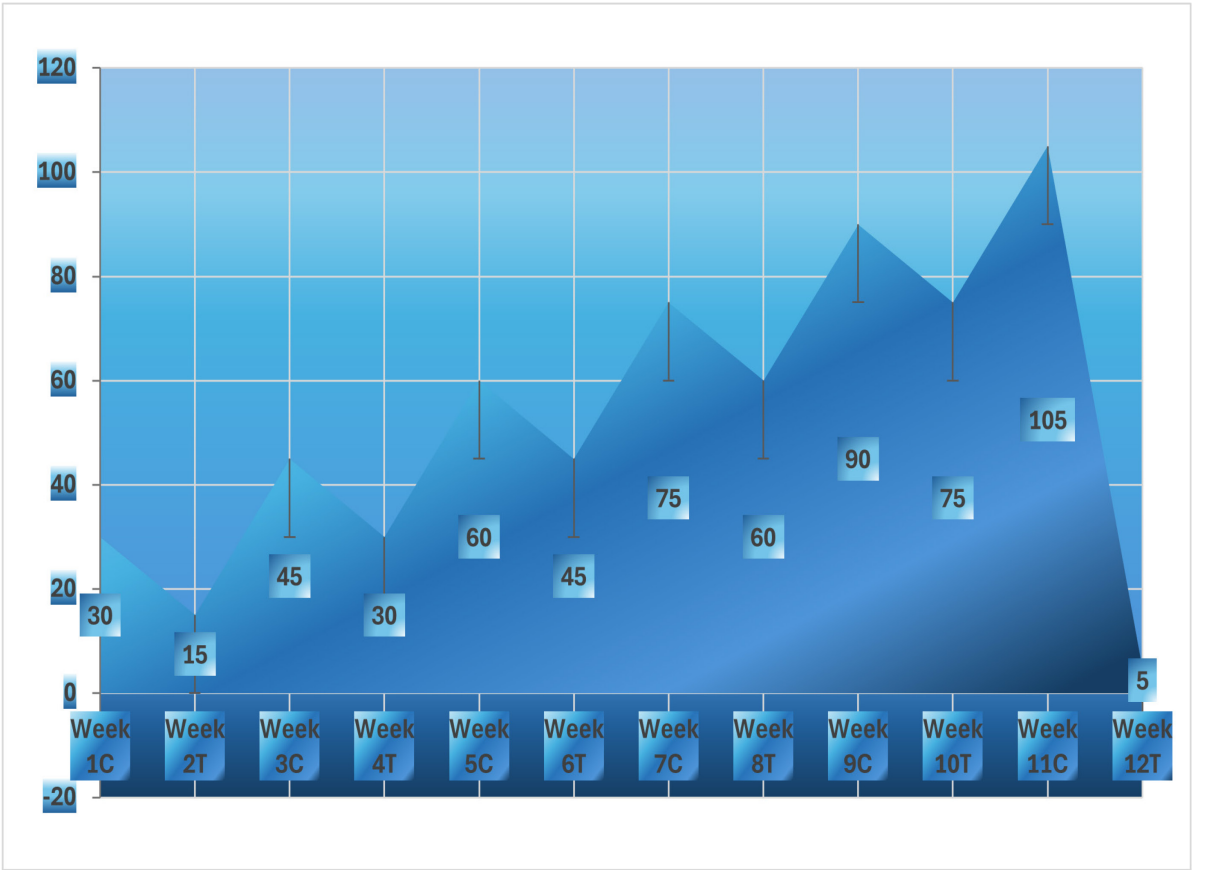
Wave Power Periodization Protocol © (WPP)



Guide: This routine is inspired by both Andrey Malanichev & Kirill Sarychev who successfully utilized a simpler and similar form of wave training to achieve their powerlifting records. Like my 15P / SSCD Protocols, this one was formed by me to make mathematical sense. In individuals who do not respond to classic periodization, they will assuredly respond to Wave Power Periodization because it will allow the CNS and muscles to recover to a greater extent between exercise sessions. The same general rules of the 15P Protocol apply here, such as only choosing one exercise per muscle group to periodize per protocol cycle and performing adequate warmups pre-workout, alongside using pyramid-up sets selfsame to those described in the 15P Protocol (increments of 15%). This is another protocol for ET:SS training. Don't forget your Steady-State Cardio on your off days, or in the mornings on your strength days.

If you find yourself failing a planned percentage lift, return to Week 1C and work your way back up to the designated percentage patiently.

Nomenclature: Crest = Overload, Trough = Deload, Amplitude Reset = Detraining.

- WEEK 1: CREST: 30% 1RM SINGLE / 6-WORKING SETS, 2-SETS TO REACH 30%. [SET 1: 15% SINGLE, SET 2-3-4-5-6: 30% SINGLE]
- WEEK 2: TROUGH: 15% 1RM SINGLE / 7-WORKING SETS, 1-SET TO REACH 15%. [SET 1-2-3-4-5-6-7: 15% SINGLE]
- WEEK 3: CREST: 45% 1RM SINGLE / 5-WORKING SETS, 3-SETS TO REACH 45%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3-4-5-6-7: 45% SINGLE]
- WEEK 4: TROUGH: 30% 1RM SINGLE / 6-WORKING SETS, 2-SETS TO REACH 30%. [SET 1: 15% SINGLE, SET 2-3-4-5-6: 30% SINGLE]
- WEEK 5: CREST: 60% 1RM SINGLES / 4-WORKING SETS, 4-SETS TO REACH 60%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3: 45% SINGLE, SET 4-5-6-7: 60% SINGLE]
- WEEK 6: TROUGH: 45% 1RM SINGLE / 5-WORKING SETS, 3-SETS TO REACH 45%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3-4-5-6-7: 45% SINGLE]
- WEEK 7: CREST: 75% 1RM SINGLE / 3-WORKING SETS, 5-SETS TO REACH 75%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3: 45% SINGLE, SET 4: 60% SINGLE, SET 5-6-7: 75% SINGLE]
- WEEK 8: TROUGH: 60% 1RM SINGLES / 4-WORKING SETS, 4-SETS TO REACH 60%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3: 45% SINGLE, SET 4-5-6-7: 60% SINGLE]
- WEEK 9: CREST: 90% 1RM SINGLE / 2-WORKING SETS, 6-SETS TO REACH 90%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3: 45% SINGLE, SET 4: 60% SINGLE, SET 5: 75% SINGLE, SET 6-7: 90% SINGLE]
- WEEK 10: TROUGH: 75% 1RM SINGLE / 3-WORKING SETS, 5-SETS TO REACH 75%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3: 45% SINGLE, SET 4: 60% SINGLE, SET 5-6-7: 75% SINGLE]
- WEEK 11: CREST: 105% 1RM SINGLE / 1-WORKING SET, 7-SETS TO REACH 105%. [SET 1: 15% SINGLE, SET 2: 30% SINGLE, SET 3: 45% SINGLE, SET 4: 60% SINGLE, SET 5: 75% SINGLE, SET 6: 90% SINGLE, SET 7: 105% SINGLE]
- WEEK 12: EQUILIBRIUM (MYONUCLEI) RESET: 5% 1RM, 1-WORKING SET TO LACTIC ACID OR MOTOR UNIT FAILURE, AND EXTENDED DETRAINING.

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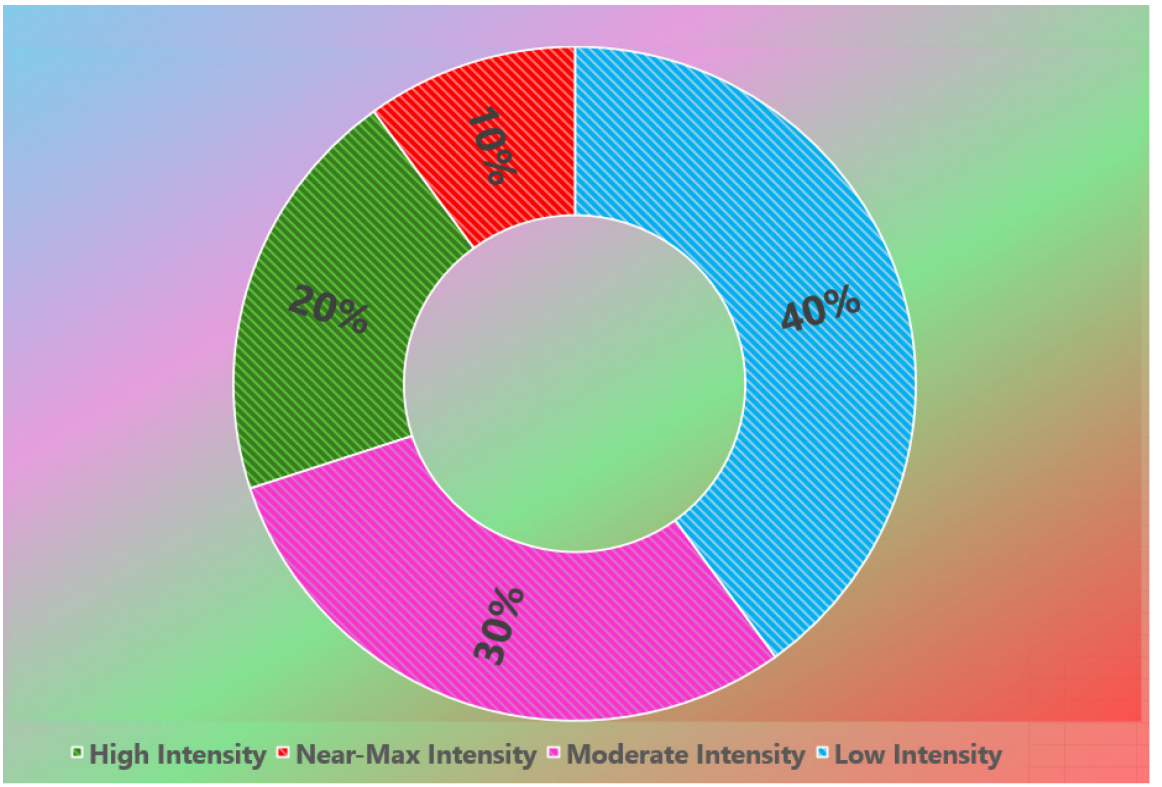
Steady-State Cardio Duration Protocol © (SSCD)



Background: I have devised this focused cardiorespiratory training protocol for the cardiovascular exercise-inclined individuals, those who have mental deficits, or those who are on a Lipolytic Phase and enjoy intensity changes and mental challenges, although this is not an Endurance Protocol, or the best workout protocol to promote fat loss. There are four intensities, you may reduce the BPM Range *Intensities* if you are elderly / out of shape or increase the BPM intensity jumps if you are an athlete.

In the polar area chart above is the Exercise Volume x BPM Range intensity breakdown of my SSCD protocol.

Guide: On Mondays and Thursdays (marked by asterisks) you will test your new Duration Max, i.e. you will test your endurance, or more precisely you will test your endurance at a certain steady-state heart rate.

The Bicycle / Handcycle are two ideal examples of lower / upper body cardio exercises that you can use with this protocol whereas nearly any other piece of cardio equipment will work, if they are not full body exercises, such that boxing without footwork or rowing with immobile legs would be considered upper body cardio, whereas using an Elliptical machine with your arms and legs simultaneously would be considered full body

cardio. I will reiterate; The cardio exercises you choose *must not* be full-body movements, as the muscles need time to recover between workouts.
Duration Max (DM) describes the longest amount of time you have gone while maintaining a Steady-State Heart Rate during an exercise, with the Duration Goal being to increase your muscle & cardiovascular endurance by overcoming your previous times, thereby facilitating lipolysis and neurological lactate-induced angiogenesis.

There are no rest periods permitted intra-workout on the SSCD protocol. If you stop due to fatigue, your new DM is reflected by the exact time you stopped (short bathroom breaks are permitted).

In terms of Duration Goals, once one duration goal is met, it should be maintained even if it becomes easy until all other BPM (Heart Rate) Intensity Duration Goals are completed. Once you have completed all Duration Goals, assuming that they were difficult to achieve, and your BPM Intensities were not changed to make your workouts too easy, and assuming you accomplished your goal of either boosting your cognition through enhanced brain angiogenesis, or burning a sufficient amount of adipose tissue, or a combination of both, you should consider transitioning to an ARCS protocol for a few months with increased consumption of carbohydrates and essential fat in your diet to focus on building muscle as there will be a tremendous cardiovascular & neurological health carryover, for what I suspect to be between two and four months.

I am against using classic Rowing Machines as upper body cardio, as the form of resistance they offer is *dynamic* quarter-reps and therefore overly damaging to the posterior chain i.e. the tension of a classic rowing machine is maximal during the beginning of the stroke and decreasing rapidly during the mid-late stroke), this leads to overtraining of the biceps. Consider attaching a resistance band with handles to a rowing machine and using them instead.

Because our upper body muscles are smaller and less conditioned than our lower body muscles, deviations of intra-workout BPM are to be expected during upper body cardio.

Finally, it is important to explain that this protocol works best with bicycles, recumbent bikes, stair steppers, handcycles, or other exercise machines that offer the ability to change gears, or resistance level. During an SSCD workout it will often be necessary to either *slightly* increase or decrease the resistance level to maintain the designated BPM range. Do not use such low resistance levels that force you to move explosively during lower intensity workouts, and do not use such high resistance levels that cause early lactic acid, motor unit, or glycogen exhaustion failure unless during Max Intensity sessions.

Time Guide: Every Monday and Thursday you will attempt to break your previous Duration Max. On Tuesday, Wednesday, and Friday you will perform exactly <u>half</u> of your current Duration Max for these sessions.
Protocol Elaboration: Total rest days are dependent on exercise intensity, therefore your hardest (highest intensity: highest resistance) workouts will have the longest amount of

programmed rest days for damaged muscles, whereas your easiest (lowest intensity: lowest resistance) workouts will have no programmed rest days between workouts.

Nobody can maintain an exact heart rate for extended periods of time, therefore fluctuations of 5 +/- BPM are expected and allowed for the duration of the workout.

Upper-body Cardio workouts should always be of a lower intensity & duration because smaller muscles must exert more force than their counterparts to train the heart at similar intensities.

The ultimate Duration Goals and BPM ranges I suggest below are for younger athletes. If you are not an amateur or professional athlete, you will need to decrease the BPM ranges to suit your comfort level and cardiovascular thresholds, but try not to decrease the duration goals, which I believe are achievable for any able-bodied adult of any age.

This protocol involves overtraining, but it is carefully planned, and injury is not to be expected unless a preexisting condition is present. If you are on an Anti-Cycle it would be wise to decrease the BPM ranges by 15BPM each intensity level to enforce undertraining (except if you're elderly and training with super low BPM ranges).

Because intramuscular lactic acid will not form as readily if your blood sugar is high during exercise, do not carbohydrate load before workouts on a Pro-Inflammation Cycle, you want your workouts to be painful, to ensure a large amount of lactic acid forms during exercise and reaches the muscles, brain, & heart, forming new blood vessels and delaying aging in the process.

Remember that thorough Resistance Training Warmups should be performed before every workout, to prevent muscle atrophy and capillary regression in the untrained parts of muscle groups, & to magnify myogenesis. If you do not have sufficient time in your day to allot to warmups, consider at least performing them before the Monday and Thursday workouts.

If you don't want to engage in cardiovascular exercise with both the upper and the lower body each week, you can specialize with ARCS, and easily replace the upper or lower body cardio days with upper or lower body resistance training by replacing intensity for loads, and periodize these resistance loads based upon the BPM intensity jumps, such that you will be engaging in high load, moderate load, low load, and very low load resistance training days. I do not suggest lifting above 60% your 1RM on resistance training days to avoid injury, or to use Extreme Tempo Training on this protocol as the goal of it is not absolute strength (See: Detraining, Deloading, & Vascular Deconditioning section for IMC Recovery Periods and 1RM Percentages). I also do not suggest alternating between resistance training and cardio training for a muscle group every week or every other week as that would defeat the purpose of this protocol, which is to enhance endurance and lipolysis through thoughtfully programmed exercise. If growing heavier in the upper body is not feasible to you because you are a professional cyclist, runner, or sprinter, you can train your upper body muscles with only Isometrics to avoid growing large amounts of unnecessary muscle mass.

For those who have no time for high frequency training, try scheduling one workout a week on an off day, and increase every duration goal thus turning your one day a week SSCD workouts into marathon-like workouts. There is *always* time to squeeze a workout or two into the week, even if you are seemingly perpetually busy, but you will need to make the limited workouts you have count.

If you are on a Pro-Inflammation Cycle consider performing 5-Sets x 50 Seconds of Occlusion Training at the end of each SSCD workout on your cardio apparatus at a low-moderate level of resistance to enhance myogenesis and angiogenesis post-workout, this would be *cardio-specific occlusion training*.

When you reach all of your Duration Goals (assuming they were not easy to achieve), you should spend between one to three months solely resistance training your cardio-trained muscles to make them stronger and more resilient to injury. The cardiovascular health accrued during an extended and successful SSCD Protocol will surely carry over to the next few months, although my idea of *cardio-carryover* is hypothetical only.

Finally, it is not intelligent to attempt to engage in a true Max Intensity (Max Heart Rate) extended steady-state cardio workout, that would be equivalent to lifting your one rep max in a single set multiple times in a row without proper rest. If you enjoy training your Max Heart Rate, do it in intervals of a minute or less, and make the workouts short (low volume), to avoid risking unnecessary cardiovascular or musculoskeletal damage.

Age-adjusted BPM Ranges: If you follow my Alpha Template directly, *Every Ten Years* starting from the Ages 18-30 Template, subtract 15 BPM from each BPM Intensity DM Range to reflect the natural aging process of your heart until age 40 after which you should attempt to maintain the decreased BPM Ranges until death. If you are very fit and healthy, subtract 5 BPM every ten years from each BPM Range starting at Alpha, and if you're a professional athlete or wish to become one, ignore age-adjusted BPM ranges entirely and base your SSCD template solely around your recently recorded max heart rate, wherein you should subtract 15BPM from that number and place it as your Near Max Intensity BPM Range, then subtract another 15BPM for each decreased intensity level.

If you train your cardiovascular system hard and with high frequency, it will adapt, therefore age-adjusted BPM ranges will likely be inaccurate because your heart will be impressively conditioned and defy aging, and programmed undertraining is liable to occur, which is suitable for promoting general health and lipolysis, but not for reaching your cardiovascular potential.

Remember that these are only templates, you can set your Max Intensity DM BPM Range to any (reasonable) number and then build back from there or change the Duration Goals. Below are my ideal SSCD Templates for *average* gymgoers, demonstrating age-adjusted training (-15 BPM decrease / 10-Years) to parallel predicted losses in cardiorespiratory fitness. If you take cardiovascular training seriously and do not neglect your diet,

supplementation, or sleep, you can likely remain on the Gamma Template until the day you die.

Finally, consider incorporating *Intermittent Sleep Scheduling* into your workout routine to make time for Endurance Training on your busy days.

IMPORTANT: Please take note of a few important Sweat Loss Nutrients that will affect muscle force generation: Potassium Chloride, Sodium, B-Vitamins, Calcium, & Zinc.

BASE SSCD PROTOCOL

ALPHA SSCD TEMPLATE (AGES 20-35)

CURRENT LOWER BODY CARDIO DURATION MAX'S (DM)
4X LOW INTENSITY DM (130BPM +/- 5) [GOAL: 240MINS]:
3X MODERATE INTENSITY DM (145BPM +/- 5) [GOAL: 180MINS]:
2X HIGH INTENSITY DM (160BPM +/- 5) [GOAL: 120MINS]:
1X NEAR MAX INTENSITY DM (175BPM +/- 5) [GOAL: 60MINS]:

CURRENT UPPER BODY CARDIO DURATION MAX'S (DM)
4X LOW INTENSITY DM (115BPM +/- 5) [GOAL: 240MINS]:
3X MODERATE INTENSITY DM (130BPM +/- 5) [GOAL: 180MINS]:
2X HIGH INTENSITY DM (145BPM +/- 5) [GOAL: 120MINS]:
1X NEAR MAX INTENSITY DM (160BPM +/- 5) [GOAL: 60MINS]:

GAMMA SSCD TEMPLATE (AGES 35-50: -15BPM)

CURRENT LOWER BODY CARDIO DURATION MAX'S (DM)
4X LOW INTENSITY DM (115BPM +/- 5) [GOAL: 240MINS]:
3X MODERATE INTENSITY DM (130BPM +/- 5) [GOAL: 180MINS]:
2X HIGH INTENSITY DM (145BPM +/- 5) [GOAL: 120MINS]:
1X NEAR MAX INTENSITY DM (160BPM +/- 5) [GOAL: 60MINS]:

CURRENT UPPER BODY CARDIO DURATION MAX'S (DM)
4X LOW INTENSITY DM (100BPM +/- 5) [GOAL: 240MINS]:
3X MODERATE INTENSITY DM (115BPM +/- 5) [GOAL: 180MINS]:
2X HIGH INTENSITY DM (130BPM +/- 5) [GOAL: 120MINS]:
1X NEAR MAX INTENSITY DM (145BPM +/- 5) [GOAL: 60MINS]:

DELTA SSCD TEMPLATE (AGES 50-DEATH: -15BPM)

CURRENT LOWER BODY CARDIO DURATION MAX'S (DM)
4X LOW INTENSITY DM (100BPM +/- 5) [GOAL: 240MINS]:
3X MODERATE INTENSITY DM (115BPM +/- 5) [GOAL: 180MINS]:
2X HIGH INTENSITY DM (130BPM +/- 5) [GOAL: 120MINS]:
1X NEAR MAX INTENSITY DM (145BPM +/- 5) [GOAL: 60MINS]:

CURRENT UPPER BODY CARDIO DURATION MAX'S (DM)
4X LOW INTENSITY DM (85BPM +/- 5) [GOAL: 240MINS]:
3X MODERATE INTENSITY DM (100BPM +/- 5) [GOAL: 180MINS]:
2X HIGH INTENSITY DM (115BPM +/- 5) [GOAL: 120MINS]:
1X NEAR MAX INTENSITY DM (130BPM +/- 5) [GOAL: 60MINS]:

>>>>>↓↓CAUTION: MAY CAUSE CARDIOVASCULAR DAMAGE↓↓<<<<<

OMEGA SSCD TEMPLATE (ENHANCED ATHLETES)
Not recommended for recreational athletes

CURRENT LOWER BODY CARDIO DURATION MAX'S (DM)
4X LOW INTENSITY DM (145BPM +/- 5) [GOAL: 240MINS]:
3X MODERATE INTENSITY DM (160BPM +/- 5) [GOAL: 120MINS]:
2X HIGH INTENSITY DM (175BPM +/- 5) [GOAL: 60MINS]:
1X MAX INTENSITY DM (190BPM +/- 5) [GOAL: 30MINS]:

CURRENT UPPER BODY CARDIO DURATION MAX'S (DM)
4X LOW INTENSITY DM (130BPM +/- 5) [GOAL: 240MINS]:
3X MODERATE INTENSITY DM (145BPM +/- 5) [GOAL: 120MINS]:
2X HIGH INTENSITY DM (160BPM +/- 5) [GOAL: 60MINS]:
1X MAX INTENSITY DM (175BPM +/- 5) [GOAL: 30MINS]:

TRIFORTE SSCD PROTOCOL

For those who are young, extremely athletic, enjoy living on the edge with the highest intensities (power), or have less free time in their days, I have prepared this protocol for you. The goal of this variation of SSCD is to reach the highest intensities of cardiovascular exercise possible, slowly, & safely, beginning with Cycle-1 with volume, moving on to Cycle-2 with volume + intensity, and finishing with Cycle-3 which is pure intensity and power. One will only move on to another cycle after having completed each

DM Goal within the current cycle. After they have completed all three cycles they should switch to the 15P, or any Classical Strength Training protocol with only 60% Max He art Rate Steady-State Cardio performed to focus almost entirely on myogenesis, for a period of one-three months, before returning to a specialization in cardio training.

The first two cycles serve the primary role of preparing the heart, muscles, and mind for the intensity to come, they are purposefully designed with moderate volume to result in a slightly more anabolic rather than adaptive response from your training, this is to ensure that your cardio-related soft tissue (muscles, tendons, joints, & cartilage) are not overly damaged leading up the Cycle-3, to thereby reduce your chances of injury.

If you have less time your day to allot to cardio, Cycle-2 or 3 may just be the best versions of SSCD for you, considering they blend intensity with efficiency perfectly, although maintaining either one for extended periods of time will increase your risk of injury due to the intensity entailed, thus the issue becomes one of longevity; how long can you maintain high intensities (high resistances, even microreps) before you experience biomechanical failure? Ideally you should at some point in your life focus on primarily endurance training when time is freed, as it's the most sustainable, angiogenic, lipolytic, and healthy way to train cardio.

Remember you can adjust the BPM Ranges, but doing so would defeat the progressive adaptation and difficulty inherent within this protocol variation. Regardless, you can reduce the final Max Intensity BPM Range of Cycle-3 by 5-10 BPM if it is necessary.

Note: I Refer to Cycle-3 as *Power* because increased resistance will be required to achieve the highest BPM Ranges. Although one could hypothetically engage in SSCD by jogging, and sprinting, or explosivity, would result in extremely high BPM Ranges being reached, unless you're a professional long distance sprinter, it's far easier to use an exercise bicycle with its variable resistance choice.

↕ CYCLE-1: VOLUME

<u>CURRENT LOWER BODY CARDIO DURATION MAX'S (DM)</u>
4X LOW INTENSITY DM (115BPM +/- 5) [GOAL: 150-MINS]:
3X MODERATE INTENSITY DM (130BPM +/- 5) [GOAL: 120-MINS]:
2X HIGH INTENSITY DM (145BPM +/- 5) [GOAL: 90-MINS]:
1X NEAR-MAX INTENSITY DM (160BPM +/- 5) [GOAL: 60-MINS]:

<u>CURRENT UPPER BODY CARDIO DURATION MAX'S (DM)</u>
4X LOW INTENSITY DM (100BPM +/- 5) [GOAL: 150-MINS]:
3X MODERATE INTENSITY DM (115BPM +/- 5) [GOAL: 120-MINS]:
2X HIGH INTENSITY DM (130BPM +/- 5) [GOAL: 90-MINS]:
1X NEAR-MAX INTENSITY DM (145BPM +/- 5) [GOAL: 60-MINS]:

- **CYCLE-2: HYBRID**

CURRENT LOWER BODY CARDIO DURATION MAX'S (DM)
4X LOW INTENSITY DM (130BPM +/- 5) [GOAL: 120-MINS]:
3X MODERATE INTENSITY DM (145BPM +/- 5) [GOAL: 90-MINS]:
2X HIGH INTENSITY DM (160BPM +/- 5) [GOAL: 60-MINS]:
1X NEAR-MAX INTENSITY DM (175BPM +/- 5) [GOAL: 30-MINS]:

CURRENT UPPER BODY CARDIO DURATION MAX'S (DM)
4X LOW INTENSITY DM (115BPM +/- 5) [GOAL: 120-MINS]:
3X MODERATE INTENSITY DM (130BPM +/- 5) [GOAL: 90-MINS]:
2X HIGH INTENSITY DM (145BPM +/- 5) [GOAL: 60-MINS]:
1X NEAR-MAX INTENSITY DM (160BPM +/- 5) [GOAL: 30-MINS]

- **CYCLE-3: POWER**

CURRENT LOWER BODY CARDIO DURATION MAX'S (DM)
4X MODERATE INTENSITY DM (145BPM +/- 5) [GOAL: 60-MINS]:
3X HIGH INTENSITY DM (160BPM +/- 5) [GOAL: 45-MINS]:
2X NEAR-MAX INTENSITY DM (175BPM +/5) [GOAL: 30-MINS]:
1X MAX INTENSITY DM (190BPM +/-5) [GOAL: 15-MINS]:

CURRENT UPPER BODY CARDIO DURATION MAX'S (DM)
4X MODERATE INTENSITY DM (130BPM +/- 5) [GOAL: 60-MINS]:
3X HIGH INTENSITY DM (145BPM +/- 5) [GOAL: 45-MINS]:
2X NEAR-MAX INTENSITY DM (160BPM +/- 5) [GOAL: 30-MINS]:
1X MAX INTENSITY DM (175BPM +/- 5) [GOAL: 15-MINS]:

continued on next page

SSCD WORKOUT SPLIT:

LB = Lower Body SSCD Cardio or Resistance Training.
UP = Upper Body SSCD Cardio or Resistance Training.

- WEEK 1:
  N-/MAX: *MON*: UB.
  LOW: TUE/WED/*THU*/FRI: LB.
  (FRI: EXTREME UPPER-BODY STRECHING)

- WEEK 2:
  MOD: *MON*/WED/FRI: LB.
  HIGH: TUE/*THU*: UB.

- WEEK 3:
  MOD: *MON*/WED/FRI: UB.
  HIGH: TUE/*THU*: LB.

- WEEK 4:
  N-/MAX: *MON*: LB.
  LOW: TUE/WED/*THU*/FRI: UB.
  (FRI: EXTREME LOWER-BODY STRECHING)

- WEEK 5:
  MOD: *MON*/WED/FRI: UB.
  HIGH: TUE/*THU*: LB.

- WEEK 6:
  MOD: *MON*/WED/FRI: LB.
  HIGH: TUE/*THU*: UB.

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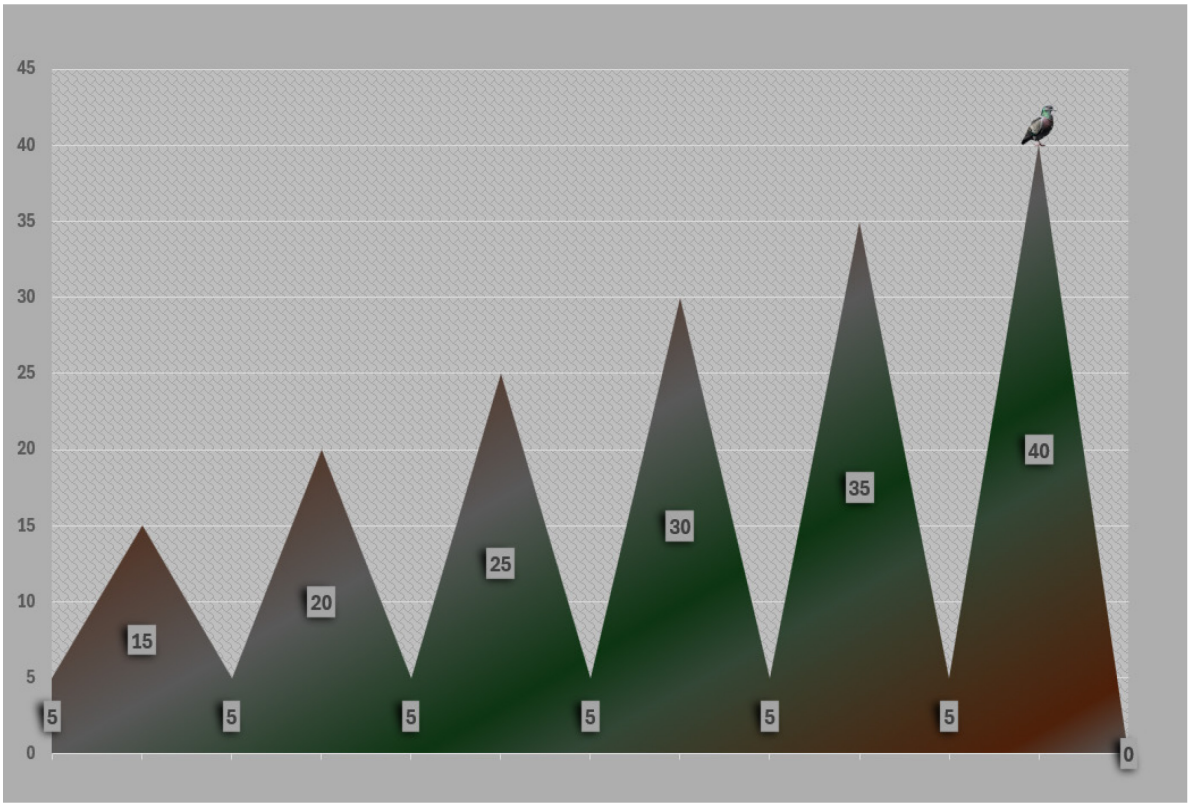
Progressive Stretch-Inspired Overload PubMed Protocol © (PSI-OP)



This Extreme Tempo Superslow Training protocol was formed both seriously and humorously, and it may be the "Holy Quail" of all exercise protocols.

Because of the high frequency of training, you will neither test nor attempt to exceed your 1RM on this protocol. If you are engaging in near-perfect ET: Superslow Training, and complete a cycle of this workout protocol, it need not be proved that your ET:SS Training 1RM has increased, so just add 2.5-5LB every cycle.

There's no point in combining high load training with a protocol designed around periodized stretching as it is far more intelligent to choose one or the other, to avoid injury.

Before your Tempo workouts, you will stretch your muscles as programmed, from lightly, to intensely. This means that as this protocol progresses your stretching should become more *painful*, as you exert more force during stretching. If you aren't in severe pain, you either aren't performing the correct stretch exercises, or you're far too flexible. If you're too flexible, you need to take a break from stretching for a couple of months to regain muscle tightness.

Remember, the purpose of this protocol is progressive stretching, not resistance training as that is merely an accoutrement.

- **D4/10/16/22/28/34:** PERIODIZED ET:SS TRAINING, SIX SETS OF SINGLES. ADD 2.5-5LB TO TEMPO 1RM EVERY CYCLE.
- **D1/7/13/19/25/31/37:** OCCLUSION TRAINING: 5-SETS X 50-SECONDS VOLITIONAL FAILURE B.F.R. TRAINING OR 5-SETS X AMRAP LACTIC ACID TRAINING (5-15% REGULAR TEMPO 1RM).
- DAYS BETWEEN TEMPO DAYS AND OCCLUSION DAYS: 60% MAXIMAL HEART RATE X 60-MINUTES STEADY-STATE CARDIO.
- **D38-41:** DETRAINING.
- **D42:** LOWEST LOAD DELOADING (WARMUPS).

- **D4:** 15% 1RM + 10-MINUTES LIGHT STRETCHING.
- **D10:** 20% 1RM + 20-MINUTES LIGHT-MODERATE STRETCHING.
- **D16:** 25% 1RM + 30-MINUTES MODERATE STRECHING.
- **D22:** 30% 1RM + 40-MINUTESS MODERATE-INTENSE STRECHING.
- **D28:** 35% 1RM + 50-MINUTES INTENSE STRETCHING.
- **D34:** 40% 1RM + 60-MINUTES EXTREME STRETCHING.

D1, D2, D3, D4, D5, D6, D7, D8, D9,

D10, D11, D12, D13, D14, D15, D16,

D17, D18, D19, D20, D21, D22, D23,

D24, D25, D26, D27, D28, D29, D30,

D31, D32, D33, D34, D35, D36, D37,

D38, D39, D40, D41, D42, D43, D44

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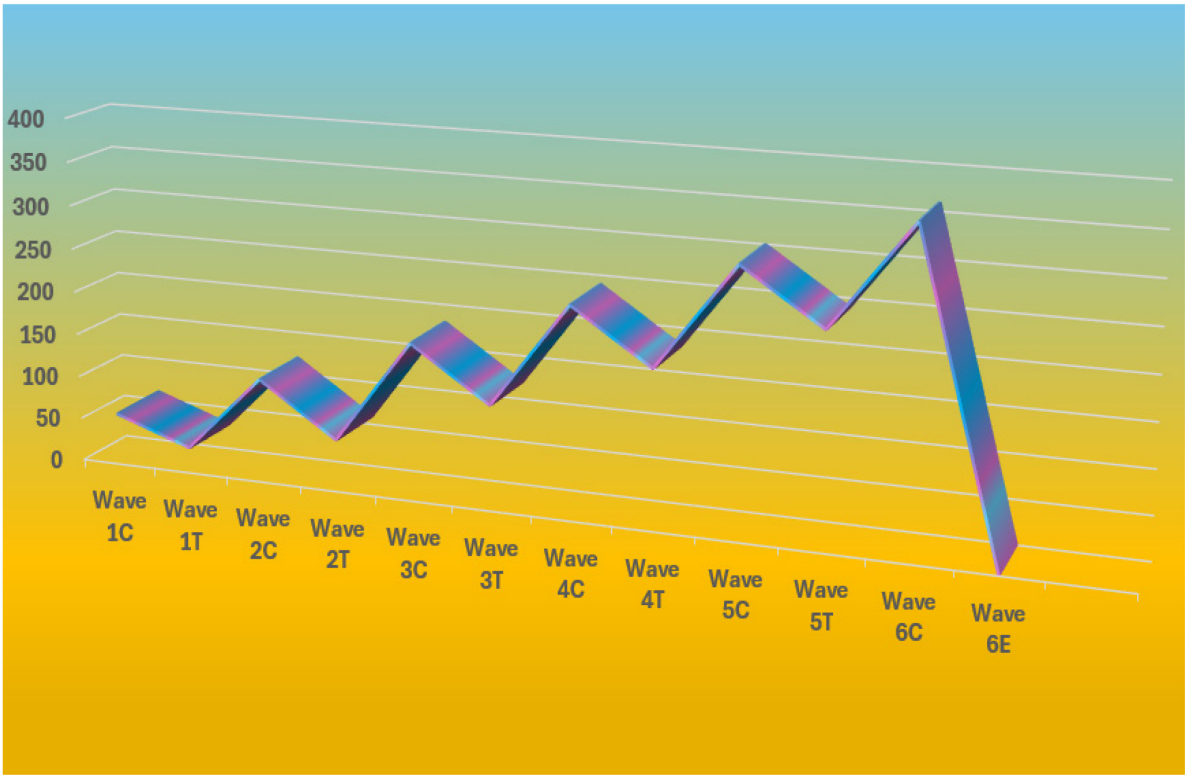
Wave Endurance Lipolysis Protocol (WEL)



This is a cardio protocol for those interested in magnifying lipolysis. It is not a protocol that involves rotating BPM (cardiovascular intensity). In terms of BPM (although resistance will vary as cardiovascular fitness increases), I consider this protocol as being more lenient (viz. 50-70% Maximum Heart Rate). Find a large BPM Range and resistance level for your cardio equipment that allows you both efficiency of movement and controlled exhaustion, a BPM Range +/- 15 that can be maintained for an hour or more without total fatigue or a breakdown in exercise form (such as needing to stop, excluding bathroom breaks, or rehydration).

Because this protocol is more lenient and not based upon BPM percentages, you can more easily incorporate upper body cardio exercises into it, and on those days you are free to train by how you feel, rather than following the times programmed.

This is a protocol designed around Inflammation, so ensure you engage in your Occlusion Training, but only do so after consulting a medical professional.

Consider also cycling between D1: Lower Body / D3: Upper Body and D1: Upper Body / D3: Lower Body after each detraining phase.

Guide: Upper Body Cardio days will be exactly half the volume-minutes of each wave, whereas Lower Body Cardio days will be equal to the volume-minutes of each wave e.g. Upper Body Cardio on WAVE 1C will be 30-Minutes.

WAVE 1C: CREST: 60-MINUTES.

- ♥ D1: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D2: OFF.
- ♥ D3: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D4: OFF.

WAVE 1T: TROUGH: 30-MINUTES.

- ♥ D5: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D6: OFF.
- ♥ D7: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D8: OFF.

WAVE 2C: CREST: 120-MINUTES.

- ♥ D9: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D10: OFF.
- ♥ D11: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D12: OFF.

WAVE 2T: TROUGH: 60-MINUTES.

- ♥ D13: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D14: OFF.
- ♥ D15: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D16: OFF

WAVE 3C: CREST: 180-MINUTES.

- ♥ D17: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D18: OFF.
- ♥ D19: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D20: OFF.

WAVE 3T: TROUGH: 120-MINUTES.

- ♥ D21: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D22: OFF.
- ♥ D23: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D24: OFF.

WAVE 4C: CREST: 240-MINUTES.

- ♥ D25: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D26: OFF.
- ♥ D27: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D28: OFF.

WAVE 4T: TROUGH: 180-MINUTES.

- ♥ D29: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D30: OFF.
- ♥ D31: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D32: OFF.

WAVE 5C: CREST: 300-MINUTES.

- ♥ D33: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D34: OFF.
- ♥ D35: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.

- D36: OFF.

WAVE 5T: TROUGH: 240-MINUTES.

- ♥ D37: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D38: OFF.
- ♥ D39: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D40: OFF.

WAVE 6C: CREST: 360-MINUTES.

- ♥ D41: LOWER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.
  - D42: OFF.
- ♥ D43: UPPER BODY SS-CARDIO>5-SETS X 50-SECONDS 80-90% OCCLUSION TRAINING ON CARDIO APPARATUS.

WAVE 6E: EQUILIBRIUM RESET.

- D44: DETRAINING. 1H EXTREME FULL-BODY STRETCHING.
- D45-46-47: DETRAINING.

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Competition Wave Cardio Protocols (CWC-E, CWC-H)

Here are templates for Endurance and High Intensity Cardio athletes who wish to experience the benefits of competition-centered Wave Periodization Cardio Training. You can set your increments at any number (percentage increases).

Effective competition training clearly requires different methods than recreation training, and that is why I have left the duration goal and max BPM empty, for in the case of both endurance races, and HIT races, race times will differ substantially.

Although competing in, and winning endurance races will be require "High Intensity" effort, I separate it in terminology from HIT, as I define HIT as focused on maximizing peak cardiac power output (the maximal cardiac pumping ability), and endurance training as maximizing slow twitch fiber growth (+ mitochondrial biogenesis) & angiogenesis.

Remember that Heart Rate-based cardio exercise protocols work most efficiently with and on exercise machines or apparatuses that allow for the frequent changing of resistance levels, and because *Resistance Level x Exercise Volume x Muscle Force = Total Cardiovascular Work*, to maintain a steady-state heart rate during any of my cardio protocols requires a semi-stable resistance levels, which as aforementioned, will of course change slightly intra-workout as the body adapts or exhausts rapidly in response to the workload, making it necessary that one increase or decrease their resistance level periodically to maintain the programmed heart rate over the entirety of the workout.

Background: Although these protocols are perfect, as they do not take into account all of the variables of training for a competition such as resistance level or speed, they are beneficial for preparing the muscles, including the heart, and the mind for competition. Endurance Training when condensed to its absolute point is a game of duration and HIT Training when condensed to its absolute point is a game of cardiovascular threshold, therefore one will find use of these designs for their simplicity, but they will surely need to be altered if you intend on becoming a master at your craft, that being competition.

Guide: Day One is your first exercise session and will be considered the <u>beginning</u> of your programmed Week. You choose the first day of your protocol, because exercise timing flexibility is an essential component of competition training.

Attempt to space out the more intensive exercise sessions evenly within each a week to allow for greater recovery between more damaging workouts, such that if you are using a protocol such as CWC-E and on Week 4, your 60% Exercise Days will be either on Mon/Wed/Fri, Tue/Thu/Sat, *or* Sun/Tue/Thu.

Days = # of exercise sessions.

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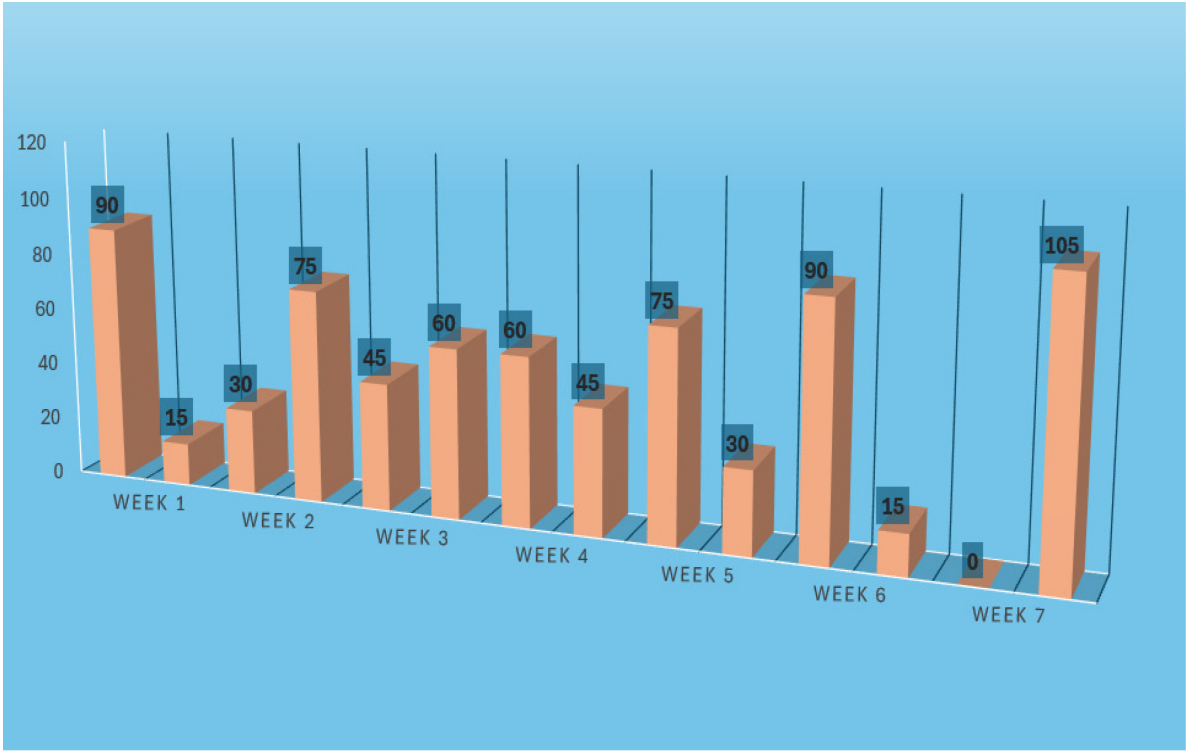
CWC-E: COMPETITION WAVE CARDIO ENDURANCE PROTOCOL ©



CWC-E is an Endurance Training protocol similar to the SSCD protocol, but there are no BPM Ranges programmed, this is because an Endurance athlete is only focused on endurance, and not cardiovascular health or power.

Because slow twitch fibers recover faster than fast twitch fibers, either because of size or blood flow differences, an Endurance athlete should train their muscles with high frequency training. This does not mean an Endurance athlete should run or swim or cycle for *thirty hours* a week, but they should steadily increase their training volume, such as an elite powerlifter will steadily and carefully increase his load every workout session, or every other workout session leading up to a competition.

Because this protocol is very high frequency, you should never attempt to "sprint" your way to the duration goal in a workout unless it is during the final 105% workout in Week 7. Your muscles will grow more enduring over time, as long as you maintain a proper speed & cadence, if you feel unwell or if you feel amazing, you can always increase your resistance or speed (if you are running or swimming) to accommodate your psyche, but do not treat training as competition, save your greatest efforts for that special day.

Endurance Training can often be harder than interval training, due to the constant need to "keep moving", without any rest permitted, and pushing yourself when you have exhausted all of your muscular and liver glycogen requires impressive determination and self-control. Nutrition must be taken more seriously during an Endurance Training protocol as you are liable to overtrain and shut down your immune system or develop severe electrolyte deficiencies.

WEEK 1:

- ♥ DAYS 1/6: 90% DURATION GOAL-MINUTES.
- ♥ DAYS 2-3-4-5: 15% DURATION GOAL-MINUTES.

WEEK 2:

- ♥ DAYS 1-2/4-5: 30% DURATION GOAL-MINUTES.
- ♥ DAYS 3/6: 75% DURATION GOAL-MINUTES.

WEEK 3:

- ♥ DAYS 1/3/5: 45% DURATION GOAL-MINUTES.
- ♥ DAYS 2/4/6: 60% DURATION GOAL-MINUTES.

WEEK 4:

- ♥ DAYS 1/3/5: 60% DURATION GOAL-MINUTES.
- ♥ DAYS 2/4/6: 45% DURATION GOAL-MINUTES.

WEEK 5:

- ♥ DAYS 1/4: 75% DURATION GOAL-MINUTES.
- ♥ DAYS 2-3/5-6: 30% DURATION GOAL-MINUTES.

WEEK 6:

- ♥ DAYS 1/4: 90% DURATION GOAL-MINUTES.
- ♥ DAYS 2-3/5-6: 15% DURATION GOAL-MINUTES.

WEEK 7:

- ♥ DAYS 1-2: DETRAINING.
- ♥ DAY 3: 105% DURATION GOAL-MINUTES.
- ♥ DAY 6: EXTREME STRETCHING.

WEEK 8:

- ♥ OCCLUSION OR LACTIC ACID TRAINING.

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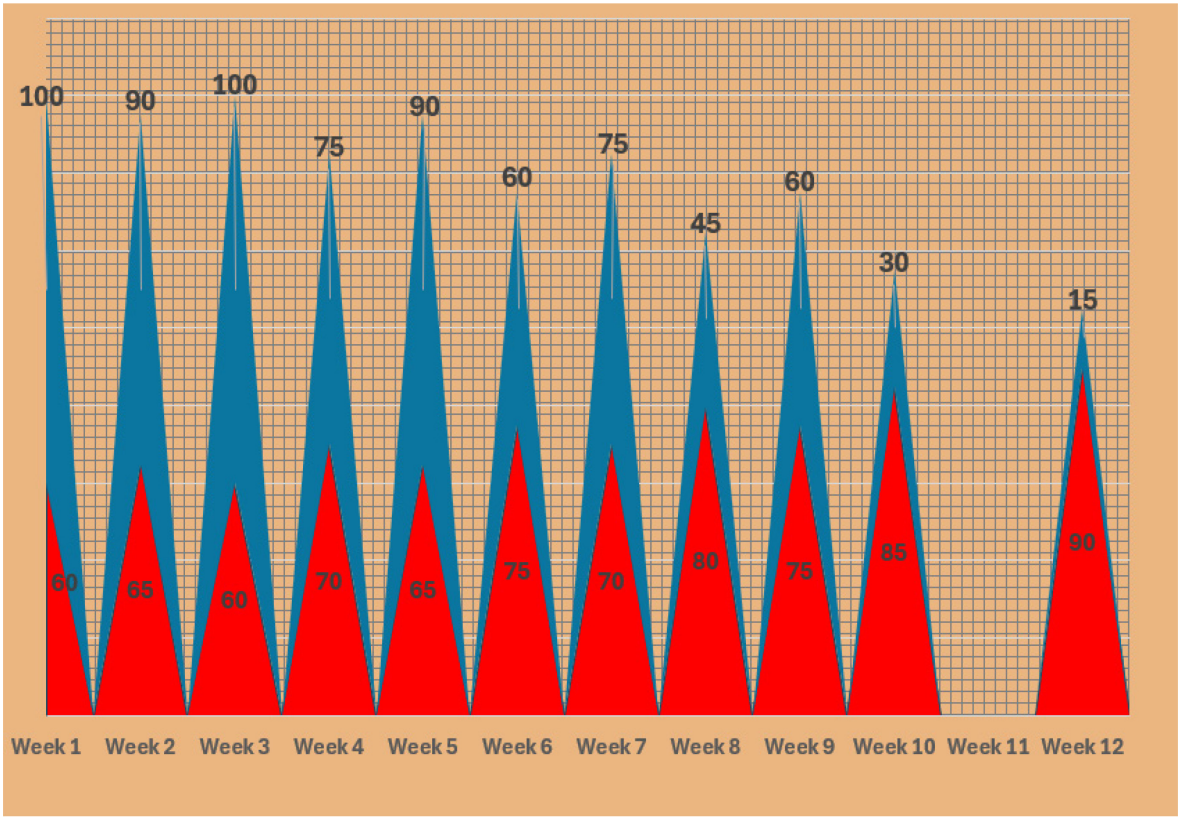
CWC-H: COMPETITION WAVE CARDIO HIT PROTOCOL ©



This protocol is best for preparing for Criteriums, Sprint Races, and any higher intensity cardiovascular race that involves a specific course, finish line, excluding Endurance Races (over one hour).

Because this protocol attaches a BPM Range to a precise distance, rather than abstract duration, where the distance will change depending on heart rate, with every successful cycle of CWC-H you perform, you should grow cardiovascularly / muscularly stronger, and faster, and your brain will be habituated to a certain specific course, or repeatable variable, such as intra-race changes to elevations, or road and track unevenness, meaning that your mind will find competition much easier, because it knows precisely when the race ends.

Importantly, this is a High Intensity Steady-state Cardio protocol, and not a High Intensity Intermittent Cardio protocol. SS-Cardio will prepare you for all possibilities—for if you experience little to no competition you can easily maintain a submaximal heart rate the entire race, but if you come up against another athlete who is far more

conditioned than you, you will be prepared to train at near-max BPM Ranges for an extended amount of time, for you will have been conditioned by the fires of Lactic Acid.

WEEK 1:

- ♥ TROUGH: DAY 1-7: 60% MAX BPM X 100% RACE DISTANCE.

WEEK 2:

- ♥ CREST: DAY 1-6: 65% MAX BPM X 90% RACE DISTANCE.

WEEK 3:

- ♥ TROUGH: DAY 1-7: 60% MAX BPM X 100% RACE DISTANCE.

WEEK 4:

- ♥ CREST: DAY 1-2-3/5-6: 70% MAX BPM X 75% RACE DISTANCE.

WEEK 5:

- ♥ TROUGH: DAY 1-6: 65% MAX BPM X 90% RACE DISTANCE.

WEEK 6:

- ♥ CREST: DAY 1-2/4-5: 75% MAX BPM X 60% RACE DISTANCE.

WEEK 7:

- ♥ TROUGH: DAY 1-2-3/5-6: 70% MAX BPM X 75% RACE DISTANCE.

WEEK 8:

- ♥ CREST: DAY 1/3/5: 80% MAX BPM X 45% RACE DISTANCE.

WEEK 9:

- ♥ TROUGH: DAY 1-2/4-5: 75% MAX BPM X 60% RACE DISTANCE.

WEEK 10:

- ♥ CREST: DAY 1/4: 85% MAX BPM X 30% RACE DISTANCE.

WEEK 11:

- ♥ TROUGH: DAY 1/4: OCCLUSION OR LACTIC ACID TRAINING + COMPETITION VISUALIZATION.

WEEK 12:

- ♥ CREST: DAY 1: 90% MAX BPM X 15% RACE DISTANCE OR **RACE DAY**.

00100010 01000100 01101111 00100000 01101110 01101111 01110100 00100000 01100111 01101111 00100000 01100111 01100101 01101110 01110100 01101100 01100101 00100000 01101001 01101110 01110100 01101111 00100000 01110100 01101000 01100001 01110100 00100000 01100111 01101111 01101111 01100100 00100000 01101110 01101001 01100111 01101000 01110100 00101100 00100000 01001111 01101100 01100100 00100000 01100001 01100111 01100101 00100000 01110011 01101000 01101111 01110101 01101100 01100100 00100000 01100010 01110101 01110010 01101110 00100000 01100001 01101110 01100100 00100000 01110010 01100001 01110110 01100101 00100000 01100001 01110100 00100000 01100011 01101100 01101111 01110011 01100101 00100000 01101111 01100110 00100000 01100100 01100001 01111001 00111011 00100000 01010010 01100001 01100111 01100101 00101100 00100000 01110010 01100001 01100111 01100101 00100000 01100001 01100111 01100001 01101001 01101110 01110011 01110100 00100000 01110100 01101000 01100101 00100000 01100100 01111001 01101001 01101110 01100111 00100000 01101111 01100110 00100000 01110100 01101000 01100101 00100000 01101000 01110100 00101110 00100010 00001010 00101101 01000100 01111001 01101100 01100001 01101110 00100000 01010100 01101000 01101111 01101101 01100001 01110011

Partial Range of Motion Overload Protocol © (PROMO)

This is a simple overload (reverse pyramid) ET:SS or Regular-speed high load resistance training protocol revolving around progressively decreasing your Range of Motion (ROM) for those who enjoy overload training (powerlifting) often, are injured, or wish to remain uninjured while *maxing out* at a high frequency. It is an especially good protocol to strengthen the CNS and therefore will be highly beneficial to powerlifters.

Protocol Guide: In the beginning of the protocol, every week the ROM will decrease, while the loads lifted will increase, thereby protecting the most sensitive parts of a muscle group and allowing overtraining to occur without unnecessary risk, and this will change to an increase in ROM every week.

The Board Press is relatively self-explanatory, but performing a Partial ROM Row is a bit more difficult to accomplish, you will need to buy a Prone Row Machine and multiple plyometric boxes or an adjustable "squat box" that when placed under you will allow you to restrict the rowing range of motion.

There will be no perfect measurement suggested of height or distance for the tools or equipment you will use to engage in this form of progressive / regressive ROM exercise as everyone has different leg and arm length, although it is necessary to ensure that the decrease or increase in ROM each week is near to 15 / 25% increments of your full ROM for each specialized exercise. This protocol can be used with isolation exercises too, do keep that in mind.

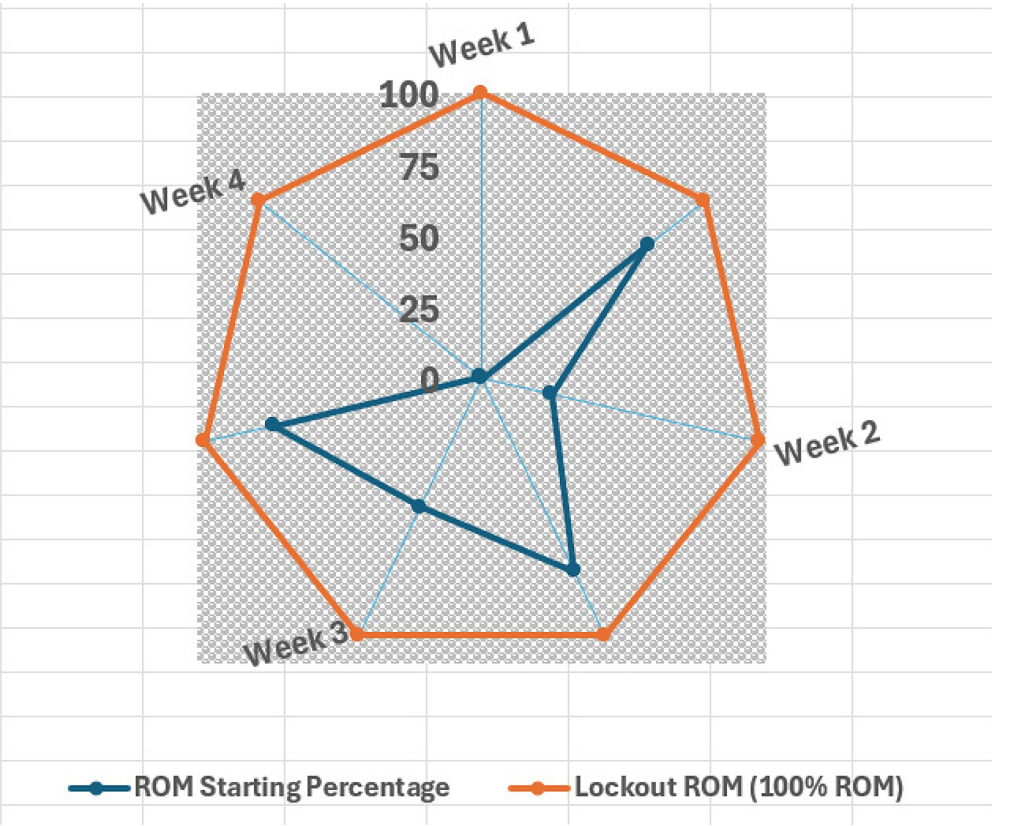
Do not conflate your partial ROM 1RM's for a Full ROM 1RM, or you will injure yourself, and when lifting with Full ROM, never exceed lifting more than 75% of your 75-100% ROM 1RM, even if you feel invincible. This means that if your Pin Bench Press 1RM is 400lbs, you should never exceed lifting more than 300lbs during your Full ROM Bench Press workouts, even if you feel invincible. Always save your hardest workouts for your decreased ROM (Partial) workouts.

This is the only strength protocol that I believe is capable of safely replacing those illogical "HIT Strength" protocols, where people attempt to combine strength with cardio by turning each set into a hysterical reps-to-failure blitzkrieg, and also speedwork, because the tendons are not maximally activated during contraction due to the decreased ROM's.

Steady-state Cardio, of course, should not be ignored, especially during periods of high load training, as the body will require enhanced blood flow to facilitate recovery processes. Because this is a full body strength routine, which many prefer, you should alternate every two or three months between lower body cardio and upper body cardio, and if you do not have access to upper body cardio machines or devices, alternate between different lower body cardio machines, such as the stair stepper, the treadmill (incline), recumbent bike, etc.

Occlusion Training can be added to each workout but make sure it's a very short workout, and very low load, consider my Incremental Occlusion Training protocol.

PROMO VARIATION A: 25% ROM INCREMENTS



CURRENT BOARD PRESS / BOX PRONE ROW 1RM'S:

(0-100% ROM) Bench Press 1RM:

(0-100% ROM) Prone Row 1RM:

(25-100% ROM) 1+1/2-Board Press 1RM:

(25-100% ROM) Low Box Row 1RM:

(50-100% ROM) 2+1/2 Board Press 1RM:

(50-100% ROM) Moderate Box Row 1RM:

(75-100% ROM) 3+1/2 Board Press 1RM:

(75-100% ROM) High Box Row 1RM:

CURRENT BOX SQUAT / BLOCK PULL 1RM'S:

(0-100% ROM) Squat 1RM:

(0-100% ROM) Deadlift 1RM:

(25-100% ROM) Low Box Squat 1RM:

(25-100% ROM) Low Block Pull 1RM:

(50-100% ROM) Moderate Box Squat 1RM:

(50-100% ROM) Moderate Block Pull 1RM:

(75-100% ROM) High Box Squat 1RM:

(75-100% ROM) High Block Pull (Rack Pull) 1RM:

WEEK 1: FULL ROM > 75-100% ROM

- DAY 1: SEVEN SETS OF STEADY-WEIGHT FULL ROM SQUAT / DEADLIFT SINGLES (DO NOT EXCEED 50% OF YOUR 75-100% ROM 1RM).
- DAY 2: SEVEN SETS OF STEADY-WEIGHT FULL ROM BENCH PRESS / PRONE ROW SINGLES. (DO NOT EXCEED 50% OF YOUR 75-100% ROM 1RM).
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: SEVEN SETS OVERLOAD SINGLES HIGH BOX SQUAT / HIGH BOX PULL.
- DAY 6: SEVEN SETS OVERLOAD SINGLES THREE BOARD PRESS / HIGH BOX PRONE ROW.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

- **WEEK 2: 25-100% ROM > 75-100% ROM**
- DAY 1: SEVEN SETS OVERLOAD SINGLES LOW BOX SQUAT / LOW BOX PULL.
- DAY 2: SEVEN SETS OVERLOAD SINGLES ONE BOARD PRESS / LOW BOX PRONE ROW.
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: SEVEN SETS OVERLOAD SINGLES HIGH BOX SQUAT / HIGH BOX PULL.
- DAY 6: SEVEN SETS OVERLOAD SINGLES THREE BOARD PRESS / HIGH BOX PRONE ROW.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

WEEK 3: 50-100% ROM > 75-100% ROM

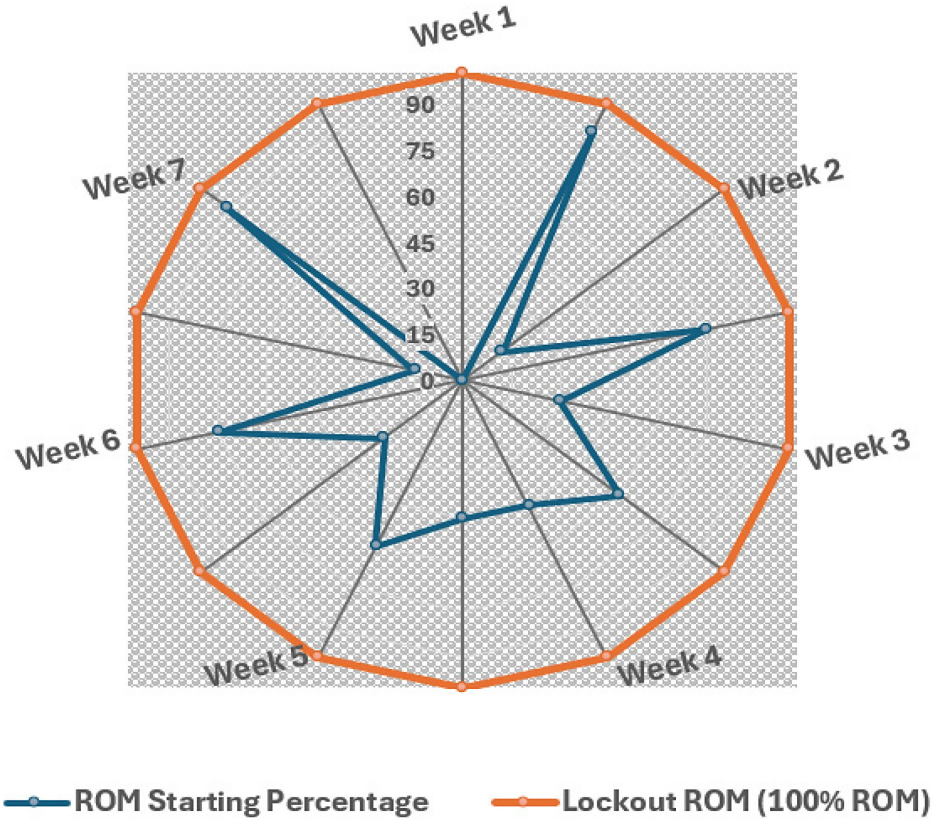
- DAY 1: SEVEN SETS OVERLOAD SINGLES MODERATE BOX SQUAT / MODERATE BOX PULL.

- DAY 2: SEVEN SETS OVERLOAD SINGLES TWO BOARD PRESS / MODERATE BOX PRONE ROW.
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: SEVEN SETS OVERLOAD SINGLES HIGH BOX SQUAT / HIGH BOX PULL.
- DAY 6: SEVEN SETS OVERLOAD SINGLES THREE BOARD PRESS / HIGH BOX PRONE ROW.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

WEEK 4: FULL ROM DELOADING

- DAY 1: LOWER BODY OCCLUSION OR LACTIC ACID TRAINING.
- DAY 2: UPPER BODY OCCLUSION OR LACTIC ACID TRAINING.
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: LOWER BODY OCCLUSION OR LACTIC ACID TRAINING.
- DAY 6: UPPER BODY OCCLUSION OR LACTIC ACID TRAINING.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

PROMO VARIATION B: 15% ROM INCREMENTS



CURRENT BOARD PRESS / BOX PRONE ROW 1RM'S:

(0-100% ROM) Bench Press 1RM:
(0-100% ROM) Prone Row 1RM:
(15-100% ROM) 1/2-Board Press 1RM:
(15-100% ROM) Very Low Box Row 1RM:
(30-100% ROM) 1-Board Press 1RM:
(30-100% ROM) Low Box Row 1RM:
(45-100% ROM) 2-Board Press 1RM:
(45-100% ROM) Low-Moderate Box Row 1RM:
(60-100% ROM) 3-Board Press 1RM:
(60-100% ROM) Moderate Box Row 1RM:
(75-100% ROM) 4-Board Press 1RM:
(75-100% ROM) High Box Row 1RM:
(90-100% ROM) 5-Board Press 1RM:
(90-100% ROM) Very High Box Row 1RM:

CURRENT BOX SQUAT / BLOCK PULL 1RM'S:

(0-100% ROM) Squat 1RM:
(0-100% ROM) Deadlift 1RM:
(15-100% ROM) Very Low Box Squat 1RM:
(15-100% ROM) Very Low Block Pull 1RM:
(30-100% ROM) Low Box Squat 1RM:
(30-100% ROM) Low Block Pull 1RM:
(45-100% ROM) Moderate Box Squat 1RM:
(45-100% ROM) Moderate Block Pull 1RM:
(60-100% ROM) Moderate-High Box Squat 1RM:
(60-100% ROM) Moderate-High Block Pull 1RM:
(75-100% ROM) High Box Squat 1RM:
(75-100% ROM) High Block Pull 1RM:
(90-100% ROM) Very High Box Squat 1RM:
(90-100% ROM) Very High Box Pull (or Rack Pull) 1RM:

WEEK 1: FULL ROM > 90-100% ROM

- DAY 1: SEVEN SETS OF STEADY-WEIGHT FULL ROM SQUAT / DEADLIFT SINGLES (DO NOT EXCEED 50% OF YOUR 75-100% ROM 1RM).
- DAY 2: SEVEN SETS OF STEADY-WEIGHT FULL ROM BENCH PRESS / PRONE ROW SINGLES. (DO NOT EXCEED 50% OF YOUR 75-100% ROM 1RM).
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: SEVEN SETS OVERLOAD SINGLES VERY HIGH BOX SQUAT / VERY HIGH BLOCK PULL.
- DAY 6: SEVEN SETS OVERLOAD SINGLES 5-BOARD PRESS / VERY HIGH BOX ROW.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

WEEK 2: 15-100% ROM > 75-100% ROM

- DAY 1: SEVEN SETS OVERLOAD SINGLES VERY LOW BOX SQUAT / VERY LOW BLOCK PULL.
- DAY 2: SEVEN SETS OVERLOAD SINGLES 1/2 BOARD PRESS / VERY LOW BOX PRONE ROW.
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: SEVEN SETS OVERLOAD SINGLES MODERATE BOX SQUAT / MODERATE BLOCK PULL.
- DAY 6: SEVEN SETS OVERLOAD SINGLES FOUR BOARD PRESS / HIGH BOX PRONE ROW.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

WEEK 3: 30-100% ROM > 60-100% ROM

- DAY 1: SEVEN SETS OVERLOAD SINGLES LOW BOX SQUAT / LOW BLOCK PULL.
- DAY 2: SEVEN SETS OVERLOAD SINGLES ONE BOARD PRESS / LOW BOX PRONE ROW.
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: SEVEN SETS OVERLOAD SINGLES MODERATE-HIGH BOX SQUAT / MODERATE-HIGH BLOCK PULL.
- DAY 6: SEVEN SETS OVERLOAD SINGLES THREE BOARD PRESS / MODERATE BOX PRONE ROW.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

WEEK 4: 45-100% ROM > 45-100% ROM

- DAY 1: SEVEN SETS OVERLOAD SINGLES MODERATE BOX SQUAT / MODERATE BLOCK PULL.
- DAY 2: SEVEN SETS OVERLOAD SINGLES TWO BOARD PRESS / LOW-MODERATE BOX PRONE ROW.
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: SEVEN SETS OVERLOAD SINGLES MODERATE BOX SQUAT / MODERATE BLOCK PULL.
- DAY 6: SEVEN SETS OVERLOAD SINGLES TWO BOARD PRESS / LOW-MODERATE BOX PRONE ROW.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

WEEK 5: 60-100% ROM > 30-100% ROM

- DAY 1: SEVEN SETS OVERLOAD SINGLES MODERATE-HIGH BOX SQUAT / MODERATE-HIGH BLOCK PULL.
- DAY 2: SEVEN SETS OVERLOAD SINGLES THREE BOARD PRESS / MODERATE BOX PRONE ROW.
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: SEVEN SETS OVERLOAD SINGLES LOW BOX SQUAT / LOW BLOCK PULL.
- DAY 6: SEVEN SETS OVERLOAD SINGLES ONE BOARD PRESS / LOW BOX PRONE ROW.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

WEEK 6: 75-100% ROM > 15-100% ROM

- DAY 1: SEVEN SETS OVERLOAD SINGLES HIGH BOX SQUAT / HIGH BLOCK PULL.
- DAY 2: SEVEN SETS OVERLOAD SINGLES FOUR BOARD PRESS / HIGH BOX PRONE ROW.
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: SEVEN SETS OVERLOAD SINGLES VERY LOW BOX SQUAT / VERY LOW BLOCK PULL.
- DAY 6: SEVEN SETS OVERLOAD SINGLES 1/2 BOARD PRESS / VERY LOW BOX PRONE ROW.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

WEEK 7: 90-100% ROM > FULL ROM

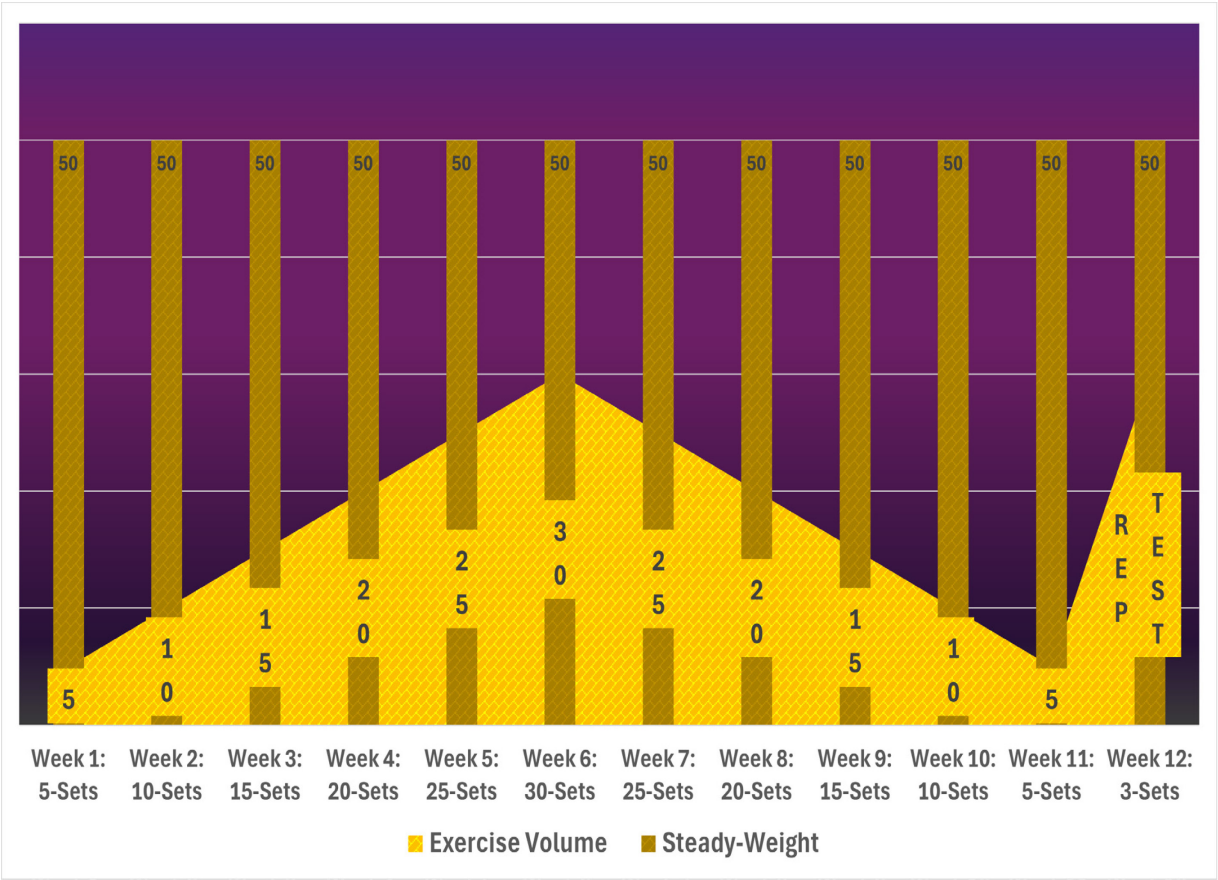
- DAY 1: SEVEN SETS OVERLOAD SINGLES VERY HIGH BOX SQUAT / VERY HIGH BLOCK PULL.
- DAY 2: SEVEN SETS OVERLOAD SINGLES 5-BOARD PRESS / VERY HIGH BOX ROW.
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: SEVEN SETS OF STEADY-WEIGHT FULL ROM SQUAT / DEADLIFT SINGLES (DO NOT EXCEED 50% OF YOUR 75-100% ROM 1RM).
- DAY 6: SEVEN SETS OF STEADY-WEIGHT FULL ROM BENCH PRESS / PRONE ROW SINGLES. (DO NOT EXCEED 50% OF YOUR 75-100% ROM 1RM).
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

WEEK 8: FULL ROM DELOADING

- DAY 1: LOWER BODY B.F.R. OR LACTIC ACID TRAINING.
- DAY 2: UPPER BODY B.F.R. OR LACTIC ACID TRAINING.
- DAY 3-4: 60MIN SS-CARDIO @ 60% MAX HR.
- DAY 5: LOWER BODY B.F.R. OR LACTIC ACID TRAINING.
- DAY 6: UPPER BODY B.F.R. OR LACTIC ACID TRAINING.
- DAY 7: 60MIN SS-CARDIO @ 60% MAX HR.

00100010 01010100 01101000 01100101 01110010 01100101 01100110 01101111 01110010 01100101 00100000 01100111 01101111 01101111 01100100 00100000 01110111 01100001 01110010 01110010 01101001 01101111 01110010 01110011 00100000 01110011 01100101 01100101 01101011 00100000 01100101 01100110 01100110 01100101 01100011 01110100 01101001 01110110 01100101 01101110 01100101 01110011 01110011 00100000 01101001 01101110 00100000 01100010 01100001 01110100 01110100 01101100 01100101 00100000 01100110 01110010 01101111 01101101 00100000 01110100 01101000 01100101 00100000 01100110 01101111 01110010 01100011 01100101 00100000 01101111 01100110 00100000 01101101 01101111 01101101 01100101 01101110 01110100 01101100 00101110 00100010 00001010 00101101 01010011 01110101 01101110 00100000 01010100 01111010 01110101

Pyramid Volume Overload (PVO) Protocol



This is a good protocol for those who prefer Regular-speed resistance training, it involves progressively increasing the total volume of programmed high load workouts using one strictly planned weight (50% 1RM: Steady-weight), starting with Undertraining (5-10 Sets), and then progressing to Optimal Training (15-20 Sets), and then Overtraining (25-30 Sets), culminating in a mirrored downward descent. This is not a protocol for any form of Tempo Training, including ET:SS or Speedwork.

For every set, and every workout, only Singles should be performed, and they should be performed as only perfect form repetitions, do not keep track of nor attempt to beat the total number of perfect form sets you achieve in each programmed workout or those of the previous weeks, just train each set to form breakdown due to motor unit failure, this allows a form of flexibility that will protect you against injuries. Every set does not need to be performed each week, but failing to complete your total programmed sets leading up to your Rep Test day will be an indication of a higher potentiality of failure.

The last week involves attempting a specific repetition goal, you have three opportunities, three sets to do so, and these are called “Attempt Sets”. If you complete

30-Perfect Form Repetitions in one set, while maintaining optimal time-under-tension, *without resting at all intra-set*, with 50% your 1RM, you can rest assured you have adequately increased your 1RM and should therefore end your workout immediately, and increase your 1RM (without testing it directly) by 5% on the following protocol reset. If you are unable to complete a perfect form Repetition Set Test, although your 1RM may have increased, you are not strong enough to add weight, and you will start over at Week-1 with the same 1RM percentage as before. One may ask why it would be necessary to *assume* a new 1RM when we can simply test it, and to that I respond in saying this is a protocol focused on volume overload, not on traditional absolute strength overload.

As for Rest Periods I would suggest 5-Minutes between sets to ensure each set is performed with a high level of focus, that is to say neurotransmitter recovery, and to stimulate mTOR to the maximal extent post-exercise.

Finally, as before, I would suggest sticking to one exercise for the entire protocol, and not incorporating other high load resistance exercises within a workout, and you can merge ARCS specialization with this protocol, or train the entire body, the choice is yours.

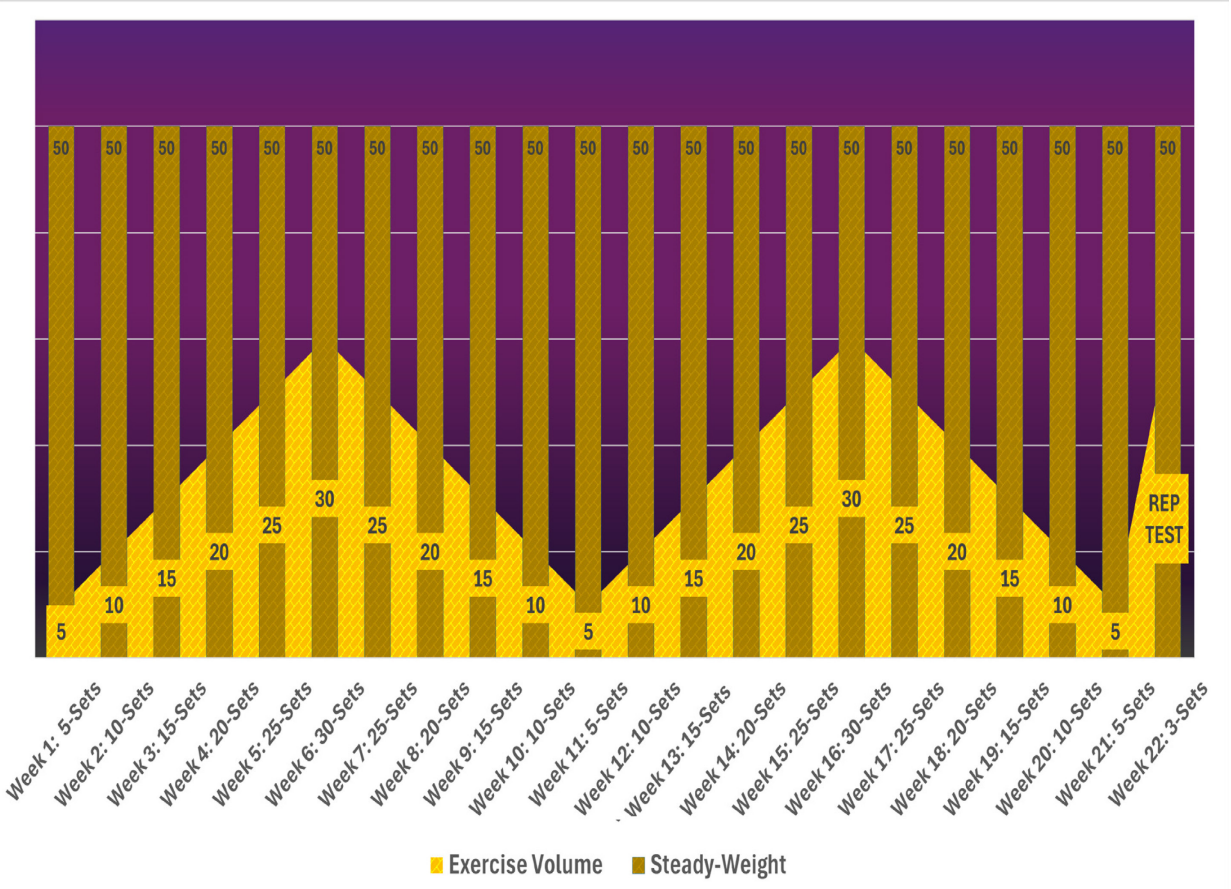
PVO Variation A: 12-Weeks

(Visualized on the previous page, suggested for the young and strong. Potential 5% 1RM increase each protocol reset)

- WEEK 1: 50% 1RM > 5-FAILURE SETS.
- WEEK 2: 50% 1RM > 10-FAILURE SETS.
- WEEK 3: 50% 1RM > 15-FAILURE SETS.
- WEEK 4: 50% 1RM > 20-FAILURE SETS.
- WEEK 5: 50% 1RM > 25-FAILURE SETS.
- WEEK 6: 50% 1RM > 30-FAILURE SETS.
- WEEK 7: 50% 1RM > 25-FAILURE SETS.
- WEEK 8: 50% 1RM > 20-FAILURE SETS.
- WEEK 9: 50% 1RM > 15-FAILURE SETS.
- WEEK 10: 50% 1RM > 10-FAILURE SETS.
- WEEK 11: 50% 1RM > 5-FAILURE SETS.
- WEEK 12: 50% 1RM > 1-3 ATTEMPT SETS x 30-REPS.

PVO Variation B: 22-Weeks

(Visualized below, suggested for novice lifters, and the elderly. Potential 5% 1RM increase each protocol reset)



- WEEK 1: 50% 1RM > 5-SETS OF SINGLES.
- WEEK 2: 50% 1RM > 10-SETS OF SINGLES.
- WEEK 3: 50% 1RM > 15-SETS OF SINGLES.
- WEEK 4: 50% 1RM > 20-SETS OF SINGLES.
- WEEK 5: 50% 1RM > 25-SETS OF SINGLES.
- WEEK 6: 50% 1RM > 30-SETS OF SINGLES.
- WEEK 7: 50% 1RM > 25-SETS OF SINGLES.
- WEEK 8: 50% 1RM > 20-SETS OF SINGLES.

- WEEK 9: 50% 1RM > 15-SETS OF SINGLES.
- WEEK 10: 50% 1RM > 10-SETS OF SINGLES.
- WEEK 11: 50% 1RM > 5-SETS OF SINGLES.
- WEEK 12: 50% 1RM > 10-SETS OF SINGLES.
- WEEK 13: 50% 1RM > 15-SETS OF SINGLES.
- WEEK 14: 50% 1RM > 20-SETS OF SINGLES.
- WEEK 15: 50% 1RM > 25-SETS OF SINGLES.
- WEEK 16: 50% 1RM > 30-SETS OF SINGLES.
- WEEK 17: 50% 1RM > 25-SETS OF SINGLES.
- WEEK 18: 50% 1RM > 20-SETS OF SINGLES.
- WEEK 19: 50% 1RM > 15-SETS OF SINGLES.
- WEEK 20: 50% 1RM > 10-SETS OF SINGLES.
- WEEK 21: 50% 1RM > 5-SETS OF SINGLES.
- WEEK 22: 50% 1RM > 1-3 ATTEMPT SETS x 30-REPS.

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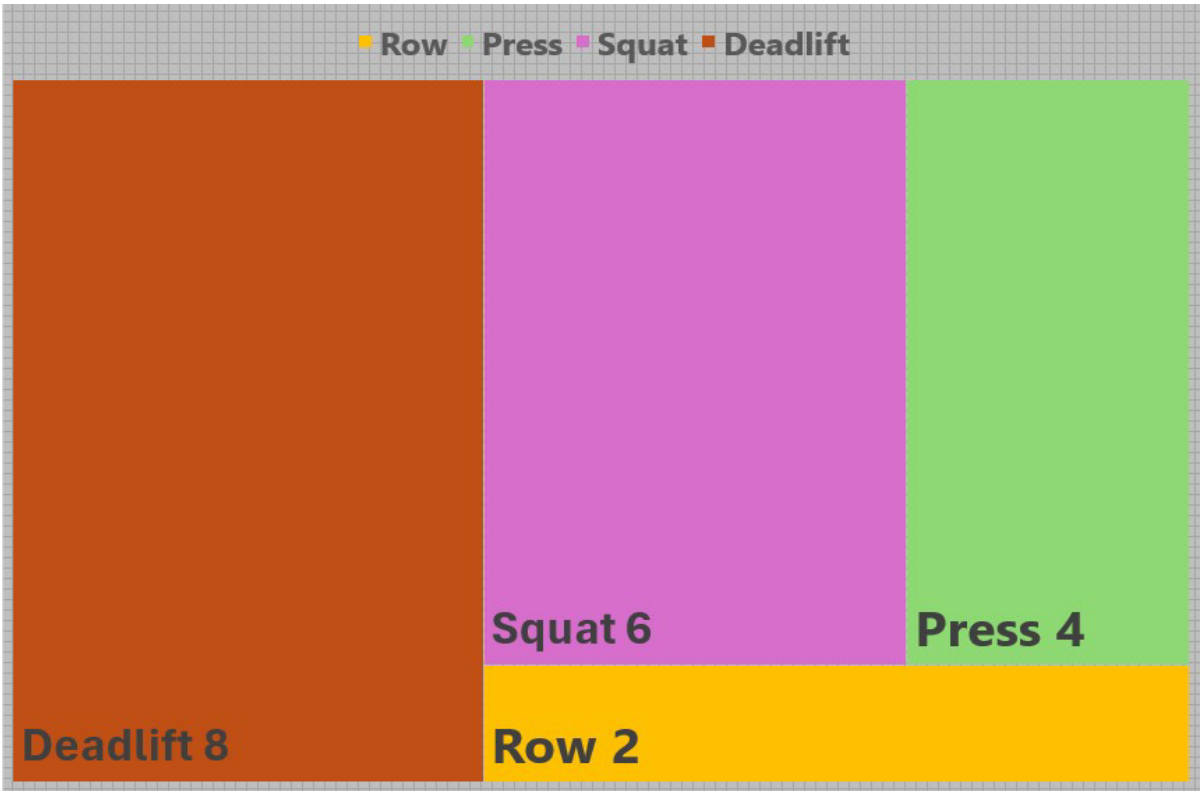
2468 Periodization Protocol



This is a fun and flexible workout protocol to play with that involves extended periodization of Olympic Barbell (Olympic Barbell only) Rowing, Bench Pressing, Squatting, and Deadlifting starting from very light weights and ending with maximal loads. The protocol is best practiced with a regular-speed tempo.

The pounds planned for each workout, for every exercise, revolve around the ratios of 65-85%, such that you will always attempt to row near 75% of your press, and squat near 75% of your deadlift, thus creating a near-perfect genetic balance of body group development.

When you fail a planned weight increase, you may attempt it for up to two more weeks in a row, but if you fail a third time, you should restart at week one for that specific lift, this is called an *Exercise Restart*, and it is an essential deloading component of this protocol.

Different lifts will always regress or progress at different speeds, at different weeks, this means that if you excel at deadlifting you may find yourself rarely Exercise Restarting your Deadlifts, but if your arms are week you may find yourself Exercise Restarting your Bench Press constantly, and this will benefit your Deadlifts as you will not be exhausting

your CNS on maximal load Bench Pressing each week, it will also benefit your Bench Press as you will be giving your arms ample time to grow through lifting lower loads.

This protocol follows a periodization scheme that is perfect for a natural athlete who prefers simpler, older types of periodization training, but the goal of this protocol is not to reach absolute strength in the most efficient way, it is a protocol to gently grow muscle mass, and absolute strength over a very safe amount of time, where Exercise Restarts will be commonplace, thereby facilitating forced deloading (undertraining), and thereby reducing the risk of injury.

Remember to maintain one grip-width or stance-width for the entirety of a periodization and avoid adding high load accessory movements to a workout.

Guide: Perform one Row, Press, Squat, and Deadlift exercise per periodization, do not change your stance, grip, stance / grip width until an Exercise Restart or completed cycle.

I will not suggest a certain rep or set range for any of the weeks as I would prefer for this exercise protocol to remain more flexible than the other strength protocols, instead I will suggest that you maintain a regular-speed reps-to-failure approach to each set, and each weight increase, during the earliest weeks, ideally accumulating as much Lactate as possible in your muscles per set. As you progress in loads, your repetitions per set will gradually decrease, until the point in time when performing more than twelve repetitions becomes too difficult, wherein you should add a moderate amount of Eccentricity (2-4 Seconds) to the highest load weeks for the remainder of the protocol or until an Exercise Reset to maintain adequate control over the weight and prevent injury, and when you reach the point in time where you find your three repetition maximum you should switch to singles.

Superslow concentricity should be saved for another workout protocol as the slow twitch fibers will be properly conditioned during the earliest aerobic and lactic acid training weeks.

As for cardio, during the earliest weeks of the protocol, if you are performing a super high number of concentric repetitions per set, and resting very little between sets, which you should be, you will be engaging in *Resistance Training Cardio*, a low-moderate intensity form of interval cardio training. This will only be possible if you train with faster tempos and train until glycogen exhaustion / lactic acid failure (reps-to-failure). Unfortunately, this form of cardio is not sufficient for the promotion of optimal physiological health, therefore you should still engage in 60-Minutes of Steady-State Cardio at 60% your Max Heart Rate with a lower body cardio exercise or upper body cardio exercise on your off days, alternating between upper and lower body cardio exercises every month or two to avoid constant overtraining of one muscle group, such as Month 1: Cycling, Month 2: Resistance Band Rowing, or you can simply change the cardio exercises for one muscle group every week or month, such as Treadmill Cardio > Stairmaster Cardio > Stationary Bicycle Cardio > Recumbent Bike Cardio. Although training a muscle group multiple times a week with Strength, Cardio, and potentially

Lactic Acid or Occlusion Training goes against ARCS, there is still a benefit and need for full body strength programs, and many individuals will prefer it over the newer alternatives I offer.

Remember to use straps or weightlifting hooks during either your deadlifts or rows depending on what type of strength you wish to develop in your forearms, if you choose to use straps during deadlifts you can train your forearms on your pressing / rowing days with the 2468 protocol (with a compound-like movement such as finger curls, conversely you may choose to only warmup your forearms on those days, and again warm them up on squatting / deadlifting days and deadlift without grip assistance to build them through isometric grip training alone.

In terms of exercise split, it would be wise to combine pressing with rowing, and squatting with deadlifting, antagonist muscles should always be trained together.

Finally, you can turn the lightest load 2468 days into secondary Occlusion Training days until you surpass 15% of your 1RM if you're on a Pro-Inflammation Cycle.

Protocol elaboration: Because Olympic Barbells are usually 45LB's, the beginning weeks of this protocol involves dumbbells (or a children's barbell) only, for the purpose of starting from a point of *very* low loads, which is especially important for building a mind-muscle connection in female / novice lifters, and as a way to engage in safe deloading in serious lifters. That means Dumbbell Presses, Dumbbell Prone Rows, Dumbbell Squats, and Dumbbell Deadlifts only. You will need Micro Plates and an assortment of dumbbells to follow this routine with greater accuracy.

Exercise Resets are going to occur for each muscle separately, which means muscle groups may be differentially aerobically, lactic acid, strength, or power trained within a week, which is a good thing, as it will allow the CNS to recover. Never attempt to increase the 1RM of all four lifts simultaneously, allow Exercise Resets to occur naturally for each body group.

If you find yourself plateauing frequently, you may need to reduce the total Load Volume of your higher load weeks. [See: Overtraining: Load Volume Tracking / Training]

- D1: 2468 PRESS > ROW.
- D2: 2468 SQUAT > DEADLIFT.
- D3-4: STEADY-STATE CARDIO.
- D5: PRESS > ROW OCCLUSION OR LACTIC ACID TRAINING.
- D6: SQUAT > DEADLIFT OCCLUSION OR LACTIC ACID TRAINING.
- D7: STEADY-STATE CARDIO.

Row – 2LB Periodization increments.
Bench – 4LB Periodization increments.
Squat – 6LB Periodizing increments
Deadlift – 8LB Periodizing increments.

↑ Note: If you memorize these increments, you will not require the week-by-week progression chart below. but it is good to visualize your growth over time and see your goals within reach.

* Begin using an Olympic Barbell, which should be at or near 45LB's in weight. In Weeks 6, 8, 11, & 22 you will begin using a classic Olympic Barbell for the designated lift and use microplates to reach the planned periodization number, or simply lift the empty barbell.

Remember to always engage in thorough warmups pre-workout!

- Week-1: 2LB Row, 4LB Press, 6LB Squat, 8LB Deadlift.
- Week-2: 4LB Row, 8LB Press, 12LB Squat, 16LB Deadlift.
- Week-3: 6LB Row, 12LB Press, 18LB Squat, 24LB Deadlift.
- Week 4: 8LB Row, 16LB Press, 24LB Squat, 32LB Deadlift.
- Week 5: 10LB Row, 20LB Press, 30LB Squat, 40LB Deadlift.
- Week 6: 12LB Row, 24LB Press, 36LB Squat, *48LB Deadlift.
- Week 7: 14LB Row, 28LB Press, 42LB Squat, 56LB Deadlift.
- Week 8: 16LB Row, 32LB Press, *48LB Squat, 64LB Deadlift.
- Week 9: 18LB Row, 36LB Press, 54LB Squat, 72LB Deadlift.
- Week 10: 20LB Row, 40LB Press, 60LB Squat, 80LB Deadlift.
- Week 11: 22LB Row, *44LB Press, 66LB Squat, 88LB Deadlift.
- Week 12: 24LB Row, 48LB Press, 72LB Squat, 96LB Deadlift.
- Week 13: 26LB Row, 52LB Press, 78LB Squat, 104LB Deadlift.
- Week 14: 28LB Row, 56LB Press, 84LB Squat, 112LB Deadlift.
- Week 15: 30LB Row, 60LB Press, 90LB Squat, 120LB Deadlift.
- Week 16: 32LB Row, 64LB Press, 96LB Squat, 128LB Deadlift.
- Week 17: 34LB Row, 68LB Press, 102LB Squat, 136LB Deadlift.
- Week 18: 36LB Row, 72LB Press, 108LB Squat, 144LB Deadlift.
- Week 19: 38LB Row, 76LB Press, 114LB Squat, 152LB Deadlift.
- Week 20: 40LB Row, 80LB Press, 120LB Squat, 160LB Deadlift.
- Week 21: 42LB Row, 84LB Press, 126LB Squat, 168LB Deadlift.
- Week 22: *44LB Row, 88LB Press, 132LB Squat, 176LB Deadlift.
- Week 23: 46LB Row, 92LB Press, 138LB Squat, 184LB Deadlift.
- Week 24: 48LB Row, 96LB Press, 144LB Squat, 192LB Deadlift.
- Week 25: 50LB Row, 100LB Press, 150LB Squat, 200LB Deadlift.
- Week 26: 52LB Row, 104LB Press, 156LB Squat, 208LB Deadlift.
- Week 27: 54LB Row, 108LB Press, 162LB Squat, 216LB Deadlift.

- Week 28: 56LB Row, 112LB Press, 168LB Squat, 224LB Deadlift.
- Week 29: 58LB Row, 116LB Press, 174LB Squat, 232LB Deadlift.
- Week 30: 60LB Row, 120LB Press, 180LB Squat, 240LB Deadlift.
- Week 31: 62LB Row, 124LB Press, 186LB Squat, 248LB Deadlift.
- Week 32: 64LB Row, 128LB Press, 192LB Squat, 256LB Deadlift.
- Week 33: 66LB Row, 132LB Press, 198LB Squat, 264LB Deadlift.
- Week 34: 68LB Row, 136LB Press, 204LB Squat, 272LB Deadlift.
- Week 35: 70LB Row, 140LB Press, 210LB Squat, 280LB Deadlift.
- Week 36: 72LB Row, 144LB Press, 216LB Squat, 288LB Deadlift.
- Week 37: 74LB Row, 148LB Press, 222LB Squat, 296LB Deadlift.
- Week 38: 76LB Row, 152LB Press, 228LB Squat, 304LB Deadlift.
- Week 39: 78LB Row, 156LB Press, 234LB Squat, 312LB Deadlift.
- Week 40: 80LB Row, 160LB Press, 240LB Squat, 320LB Deadlift.
- Week 41: 82LB Row, 164LB Press, 246LB Squat, 328LB Deadlift.
- Week 42: 84LB Row, 168LB Press, 252LB Squat, 336LB Deadlift.
- Week 43: 86LB Row, 172LB Press, 258LB Squat, 344LB Deadlift.
- Week 44: 88LB Row, 176LB Press, 264LB Squat, 352LB Deadlift.
- Week 45: 90LB Row, 180LB Press, 270LB Squat, 360LB Deadlift.
- Week 46: 92LB Row, 184LB Press, 276LB Squat, 368LB Deadlift.
- Week 47: 94LB Row, 188LB Press, 282LB Squat, 376LB Deadlift.
- Week 48: 96LB Row, 192LB Press, 288LB Squat, 384LB Deadlift.
- Week 49: 98LB Row, 196LB Press, 294LB Squat, 392LB Deadlift.
- Week 50: 100LB Row, 200LB Press, 300LB Squat, 400LB Deadlift.
- Week 51: 102LB Row, 204LB Press, 306LB Squat, 408LB Deadlift.
- Week 52: 104LB Row, 208LB Press, 312LB Squat, 416LB Deadlift.
- Week 53: 106LB Row, 212LB Press, 318LB Squat, 424LB Deadlift.
- Week 54: 108LB Row, 216LB Press, 324LB Squat, 432LB Deadlift.
- Week 55: 110LB Row, 220LB Press, 330LB Squat, 440LB Deadlift.
- Week 56: 112LB Row, 224LB Press, 336LB Squat, 448LB Deadlift.
- Week 57: 114LB Row, 228LB Press, 342LB Squat, 456LB Deadlift.
- Week 58: 116LB Row, 232LB Press, 348LB Squat, 464LB Deadlift.
- Week 59: 118LB Row, 236LB Press, 354LB Squat, 472LB Deadlift.
- Week 60: 120LB Row, 240LB Press, 360LB Squat, 480LB Deadlift.
- Week 61: 122LB Row, 244LB Press, 366LB Squat, 488LB Deadlift.
- Week 62: 124LB Row, 248LB Press, 372LB Squat, 496LB Deadlift.
- Week 63: 126LB Row, 252LB Press, 378LB Squat, 504LB Deadlift.
- Week 64: 128LB Row, 256LB Press, 384LB Squat, 512LB Deadlift.
- Week 65: 130LB Row, 260LB Press, 390LB Squat, 520LB Deadlift.
- Week 66: 132LB Row, 264LB Press, 396LB Squat, 528LB Deadlift.
- Week 67: 134LB Row, 268LB Press, 402LB Squat, 536LB Deadlift.
- Week 68: 136LB Row, 272LB Press, 408LB Squat, 544LB Deadlift.
- Week 69: 138LB Row, 276LB Press, 414LB Squat, 552LB Deadlift.
- Week 70: 140LB Row, 280LB Press, 420LB Squat, 560LB Deadlift.
- Week 71: 142LB Row, 284LB Press, 426LB Squat, 568LB Deadlift.

- Week 72: 144LB Row, 288LB Press, 432LB Squat, 576LB Deadlift.
- Week 73: 146LB Row, 292LB Press, 438LB Squat, 584LB Deadlift.
- Week 74: 148LB Row, 296LB Press, 444LB Squat, 592LB Deadlift.
- Week 75: 150LB Row, 300LB Press, 450LB Squat, 600LB Deadlift.
- Week 76: 152LB Row, 304LB Press, 456LB Squat, 608LB Deadlift.
- Week 77: 154LB Row, 308LB Press, 462LB Squat, 616LB Deadlift.
- Week 78: 156LB Row, 312LB Press, 468LB Squat, 624LB Deadlift.
- Week 79: 158LB Row, 316LB Press, 474LB Squat, 632LB Deadlift.
- Week 80: 160LB Row, 320LB Press, 480LB Squat, 640LB Deadlift.
- Week 81: 162LB Row, 324LB Press, 486LB Squat, 648LB Deadlift.
- Week 82: 164LB Row, 328LB Press, 492LB Squat, 656LB Deadlift.
- Week 83: 166LB Row, 332LB Press, 498LB Squat, 664LB Deadlift.
- Week 84: 168LB Row, 336LB Press, 504LB Squat, 672LB Deadlift.
- Week 85: 170LB Row, 340LB Press, 510LB Squat, 680LB Deadlift.
- Week 86: 172LB Row, 344LB Press, 516LB Squat, 688LB Deadlift.
- Week 87: 174LB Row, 348LB Press, 522LB Squat, 696LB Deadlift.
- Week 88: 176LB Row, 352LB Press, 528LB Squat, 704LB Deadlift.
- Week 89: 178LB Row, 356LB Press, 534LB Squat, 712LB Deadlift.
- Week 90: 180LB Row, 360LB Press, 540LB Squat, 720LB Deadlift.
- Week 91: 182LB Row, 364LB Press, 546LB Squat, 728LB Deadlift.
- Week 92: 184LB Row, 368LB Press, 552LB Squat, 736LB Deadlift.
- Week 93: 186LB Row, 372LB Press, 558LB Squat, 744LB Deadlift.
- Week 94: 188LB Row, 376LB Press, 564LB Squat, 752LB Deadlift.
- Week 95: 190LB Row, 380LB Press, 570LB Squat, 760LB Deadlift.
- Week 96: 192LB Row, 384LB Press, 576LB Squat, 768LB Deadlift.
- Week 97: 194LB Row, 388LB Press, 582LB Squat, 776LB Deadlift.
- Week 98: 196LB Row, 392LB Press, 588LB Squat, 784LB Deadlift.
- Week 99: 198LB Row, 396LB Press, 594LB Squat, 792LB Deadlift.
- Week 100: 200LB Row, 400LB Press, 600LB Squat, 800LB Deadlift.

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Variable Failure Circuit © (VFC)

Whether you are looking for a workout protocol to that can stimulate massive amounts of lactic acid in your muscles, promote angiogenesis in the absence of occlusion, rehabilitate soft tissue injuries, or you need a workout protocol designed for pure efficiency and speed, the Variable Failure Circuit is perfect for you.

Protocol Explanation: A VFC workout involves using 5% your 1RM performing exactly one set to motor unit or lactic acid failure, without resting, for between 10 to 30-Minutes, I call these sets *Lactic Set*s. Every twenty or thirty repetitions you will change your Exercise Form, thereby exhausting different parts of your muscles, but you must not rest, you must ensure your muscles are under a near-constant time-under-tension. You will continue performing your multi-variable exercise until your willpower fails, at which point you end the workout, there will be no restarts. You will keep track of the time point at which you failed, similarly to the SSCD protocol, and attempt to beat it the next week, if you continue a VFC cycle. After the point in time that you reach a 30-Minute Lactic Set *without overexerting yourself, you can add 2LB the following week, thus increasing your topical, but not actual 1RM. It may be necessary to use micro-plates, or specialized dumbbells to achieve this weight jump. Most importantly, to maintain adequate time-under-tension you must use Quarter Reps and 0-50% ROM Repetitions for

every exercise, this means you should never “lockout” the repetitions, if you do you’ll be defeating the purpose of this protocol altogether.

If by chance you have iron resolve, you should still not exceed 30-Minutes, as exceeding this time limit will lead to differential muscle adaptation (mitochondrial vs myogenic), and you’ll be approaching the territory of Endurance Training.

VFC for the upper and lower body is best paired with dumbbells, due to the ease of changing exercise form intra-set, the added difficulty inherent in free-weight exercises, and the commonality of light weight dumbbell availability. Attempting this protocol using an unloaded barbell or football bar is possible, but 30LB’s is far too heavy a weight for the sheer amount of volume that is to be performed.

This protocol will result in extreme lactic acid accumulation and escalating pain; you should therefore not attempt it if you have a low pain threshold. To maintain proper form throughout the timespan of a Lactic Set will require intense focus, and you may find it necessary to grunt to enhance your concentration and force output, because of this you should consider training at home, you’d be amazed of what you can accomplish with just a bench and a set of light weight dumbbells.

Even though this protocol utilizes low loads, due the extreme volume entailed it should only be performed at the most once per week for a muscle group.

Finally, you can perform this protocol with isolation exercises if you so choose, again preferably using dumbbells, and because of the intensity and volume of this protocol, you can consider it a form of resistance training cardiovascular exercise.

Exercise Form Variables:

Slight Incline Bench Pressing / Incline Bench Prone Rowing Exercise Form Variables: High on your chest, Low on your chest, Wide grip, Moderate grip, Close Grip, Quarter reps, Middle reps, Partial reps, Supinating, Pronating.

Squat / Deadlift Exercise Form Variables: Wide stance, Moderate stance, Close stance, Heels elevated, Toes elevated, Quarter reps, Middle reps, Partial reps, Arched back, Slouched back.

Note: “Grip” variables for dumbbell pressing or rowing is equivalent to the distance of the elbows and hands from the torso.

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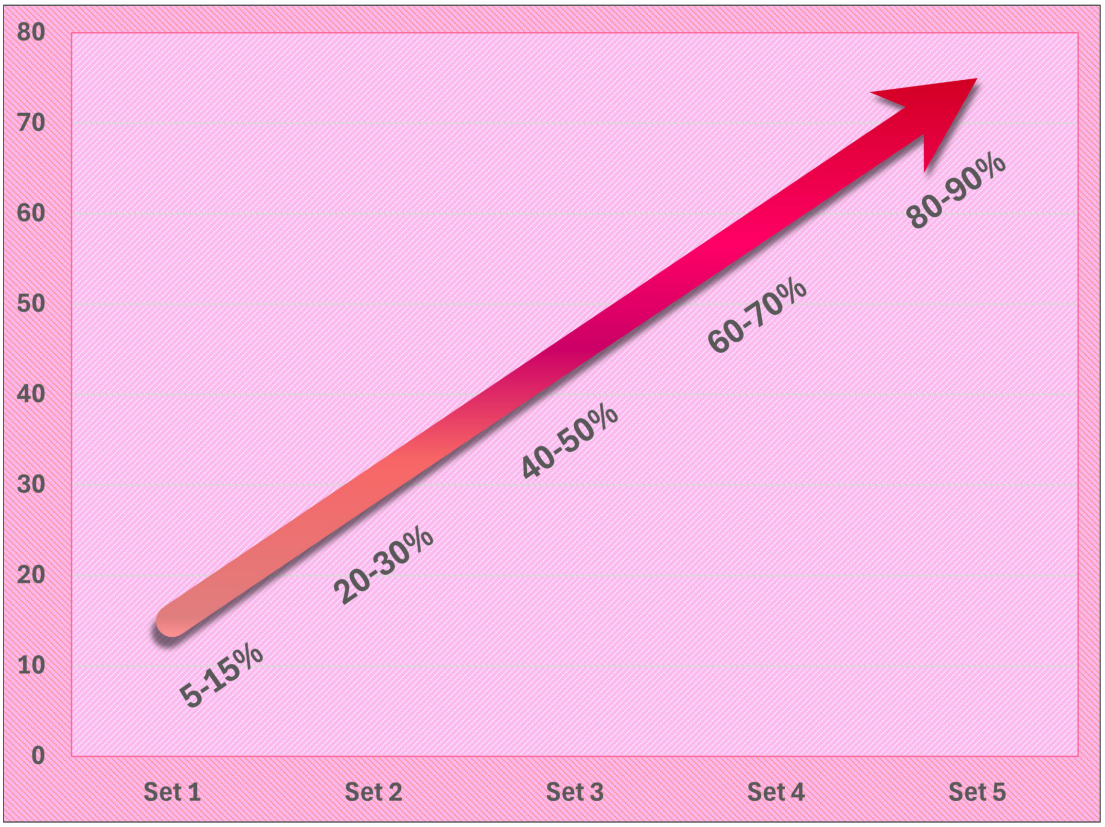
Incremental Occlusion Training © (IOT)



REDUNDANT WARNING: CONSULT WITH A QUALIFIED MEDICAL PROFESSIONAL BEFORE ATTEMPTING THIS EXERCISE PROTOCOL, AND REMEMBER THE RISKS!

Because many individuals will be unable to afford overpriced commercial B.F.R. Cuffs, the next best option, aside from simple Velcro straps, is tourniquets, but using tourniquets for Occlusion Training increases your risks for side effects because of the increased possibility of "over-occluding" a muscle. The majority of these risks will be prevented through engaging in IOT, which is an idea I have formulated to make tourniquet Occlusion Training more effective, safer, and of much greater intensity. These are highly *advanced* occlusion training protocols; therefore, they are not recommended for those with preexisting health conditions.

My favorite tourniquet for Incremental Occlusion Training and the only one I use, although the company would likely not approve of this, is the *OMNA Marine Tourniquet*, because it has a patented ratchet tightening mechanism, making it perfect for IOT. The cheaper variety of tourniquets use a twist / stick tightening mechanism thereby making them more difficult for use with IOT.

IOT Explanation: After each component set, you will quickly increase your occlusion percentage, and continue exercising, while not taking any real rest periods until you are fatigued completely from either the limb pain that accompanies occlusion training or upon reaching the designated time limit of total occlusion time. When I refer to "limb pain", I do not mean Lactic Acid pain, it is instead a specific form of pain you will only experience during Occlusion Training that will radiate from and down your limbs. Although you will never know the exact occlusion percentage for tourniquet occlusion training, you should be able to estimate the percentages after practice and by feel after a few sessions. Component Set One should be considered occlusion from a lightly tightened strap only, with no twisting, turning, or ratcheting. When all seven component sets are completed in good time, you should immediately remove your tourniquets and allow your muscles to reoxygenate.

Remember to use Compound Movements for the majority of your B.F.R. workouts to maximally stimulate Hematopoietic Stem Cells production. Also, because the ultimate goal of Occlusion Training is angiogenesis, performing machine circuits or alternating between different exercises between each IOT component set is an excellent idea. Furthermore, adding Vibration Therapy (Vibrating your Occluded muscles during your rest periods) to an IOT protocol is in my opinion a great way to facilitate angiogenesis.

Combining Occlusion Training with Post-Exercise Steady-State Cardio and targeted Deep-Tissue Massage (Shiatsu / A.R.T.) is an excellent way to magnify myogenesis and muscle angiogenesis, so too may it protect our nerves against the deleterious effects of extended hypoxia (hypothetically), but if you experience chronic numbness or tingling in your limbs in the weeks after Occlusion Training, switch immediately to an Anti-Cycle composed of frequent and concentrated Lion's Mane shakes, Vitamins, and topically applied Eucalyptus oil, to protect & regenerate your nerves.

This protocol should only be utilized for a given group of limbs at the very most, twice per week, and you should use an Interval Timer iOS / Android application to maintain the programmed set times (my favorite is the free Interval Timer Plus by Su-Au Hwang, See Page 1135 for a timer guide), *adding ten seconds extra each timed set* to give yourself the necessary time to adjust the occlusion percentage between component sets and return to your chosen exercise position.

EtOH-AnGIO Occlusion Training ©

Because this is a purely angiogenic workout protocol, it is my suggestion that one consume *low dosages* of Alcohol pre-workout, and in the following two or three hours post-workout, to not only magnify Occlusion Training-induced skeletal muscle angiogenesis, but also to exert an acute but subtle antioxidant response in musculoskeletal, cardiovascular, & neurological blood vessels, and tissue, to hypothetically mitigate or prevent any deleterious side effects of extended time and increased limb occlusion hypoxia-based exercise. This is a novel technique I have experimented with numerous times, and it is in my opinion the future of counteracting the known and as of yet unknown side effects and health complications of Occlusion Training.

In many individuals, either because of recreational drug use, supplement use, or prescription use, there is a certain decreased level of VEGF / VEGF-receptor activity in their bodies, and this in my opinion renders Occlusion Training far more dangerous to the body, as the compensatory mechanism of reoxygenation and angiogenesis will be perturbed following an occluded workout, thus leading to blood vessel damage, or increased tissue damaged. Because of this it is my suggestion that if you are older in age, or under the influence of anti-angiogenic chemicals, even vitamins for example, that you absolutely utilize alcohol intra-exercise for its impressive angiogenic-promoting purposes. So too may it be necessary to quell excess inflammation during and immediately after occluded exercise in our limbs if we are on an extended Pro-Cycle, to avoid unintentionally damaging our blood vessels or muscle fibers beyond repair due to the excessive autophagy that hypoxia or hyperthermia may cause.

I believe that for high frequency classical forms of steady-hypoxia Occlusion Training, or more precisely, severe forms of progressive-hypoxia Occlusion Training, such as Incremental Occlusion Training, it is necessary to attempt to mitigate any side effects, as for young athletes or those who are physiologically healthy with accelerated wound healing rates comes the higher rate of cellular resilience, but for those suffering from accelerated biological decay comes the inability to adapt to acute or chronic cellular stress. Thus, if low dose alcohol is not used as a *paradoxical angiogenic antioxidant*, then it is extremely unwise to engage in any form of Occlusion Training if you are not in a good biological state of stable and controlled blood pressure, and angio-potential, that being the potential to form new blood vessels rapidly and efficiently following angiogenic exercise.

Finally, because Occlusion Training is so very myogenic, your dosage of Alcohol consumed pre / post-workout may be increased slightly as the suppressive effects Alcohol exerts on early myogenesis will be partially overcome by this combination, in my hypothesis.

For recommended Alcohol dosing, consider consuming 0.125mg x kg acutely pre-workout, and consume another 0.125mg x kg slowly in the three hour period immediately following IOT exercise to suppress hypoxia-induced excessive autophagy.

Beginner IOT (Safest)

- Five Component Sets = One IOT Set.
- 1RM Percentage: 5-30% (Ideally 5%).
- Total IOT Sets: 3-Sets Recommended, 4-Sets Maximum.
- Reoxygenation Time: 5-Minutes.
- Cadence: 1-1.7 Repetitions per second.
- 2-Minute 30-Seconds Total *Time-under-Occlusion* (including +10 Seconds each set for Occlusion Adjustment).

- ⊙ Component Set 1: 5-15% Occlusion x 30-Seconds. No Limb Pain.
- ⊙ Component Set 2: 20-30% Occlusion x 25-Seconds. Low Limb Pain.
- ⊙ Component Set 3: 40-50% Occlusion x 20-Seconds. Moderate Limb Pain.
- ⊙ Component Set 4: 60-70% Occlusion x 15-Seconds. High Limb Pain.
- ⊙ Component Set 5: 80-90% Occlusion x 10-Seconds. Max Limb Pain.

Advanced IOT (Intermediate)

- Ψ Five Component Sets = One IOT Set.
- Ψ 1RM Percentage: 5-30% (Ideally 5%).
- Ψ Total IOT Sets: 2-Sets Recommended, 3-Sets Maximum.
- Ψ Reoxygenation Time: 10-Minutes.
- Ψ Cadence: 1-1.7 Repetitions per second.
- Ψ 2-Minutes 55-Seconds Total *Time-under-Occlusion* (including +10 Seconds each set for Occlusion Adjustment).

  - ⊙ Component Set 1: 5-15% Occlusion x 35-Seconds. No Limb Pain.
  - ⊙ Component Set 2: 20-30% Occlusion x 30-Seconds. Low Limb Pain.
  - ⊙ Component Set 3: 40-50% Occlusion x 25-Seconds. Moderate Limb Pain.
  - ⊙ Component Set 4: 60-70% Occlusion x 20-Seconds. High Limb Pain.
  - ⊙ Component Set 5: 80-90% Occlusion x 15-Seconds. Max Limb Pain.

Master IOT (Dangerous)

- Ψ Five Component Sets = One IOT Set.
- Ψ 1RM Percentage: 5-30% (Ideally 5%).
- Ψ Total IOT Sets: 1-Set Recommended, 2-Sets Maximum.
- Ψ Cadence: 1-1.7 Repetitions per second.
- Ψ 3-Minute 20-Seconds Total *Time-under-Occlusion* (including +10 Seconds each set for Occlusion Adjustment).

  - ⊙ Component Set 1: 5-15% Occlusion x 40-Seconds. No Limb Pain.
  - ⊙ Component Set 2: 20-30% Occlusion x 35-Seconds. Low Limb Pain.
  - ⊙ Component Set 3: 40-50% Occlusion x 30-Seconds. Moderate Limb Pain.
  - ⊙ Component Set 4: 60-70% Occlusion x 25-Seconds. High Limb Pain.
  - ⊙ Component Set 5: 80-90% Occlusion x 20-Seconds. Max Limb Pain.

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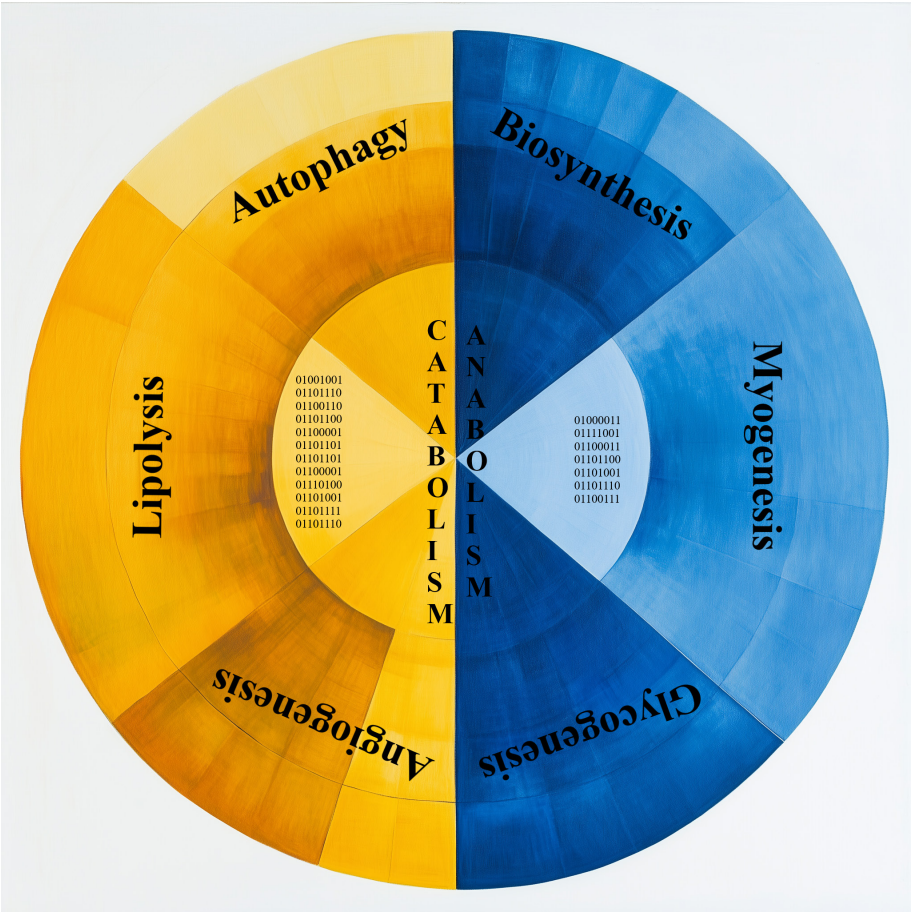
Angio-Fast Protocol © (AF)



Protocol Background: Fasting as you have learned is angiogenic and lipolytic, but muscle catabolism is a very real risk to any intermittent or prolonged fast, which is why I have designed this pro-inflammation dietary-exercise protocol, to enhance brain and muscle angiogenesis, while stimulating lipolysis. One day will be Angio-Fasting (Angiogenic Fasting), that is: Fasting, Cardio, and Occlusion Training, and the next day or days will be Strength-Refeeding. Only morning training will be permitted to rapidly deplete the bodies Glycogen stores on a fasted day, and to give the body the adequate amino acids that will be necessary for early protein synthesis on the Strength and Refeed days.

You will not need Ketone Sticks for this protocol because the primary goal of it is the promotion of systemic autophagy and angiogenesis. A high blood level of ketones does not always indicate a high level of ongoing lipolysis or autophagy.

Protocol Guide: Firstly, in the morning you will engage in Steady-state cardio to promote systemic autophagy, neurogenesis, neurological angiogenesis, cardio-induced muscular angiogenesis, and lipolysis. This cardio session will also hypothetically protect the

muscles, nerves, and blood vessels you will occlusion train from hypoxia-induced damage. Secondly, later in the day, in the late evening hours, you will engage in very low load (5-10% 1RM ideally) compound movement Occlusion Training for either the same muscle group you cardio trained (probable to be the lower body), the upper body muscle group, with different exercises each set, or the same exercises. You can train your entire body with Occlusion Training if you want to, but do not exceed 5-Sets of total Occlusion Training or the designated max IOT sets for the upper or lower body limbs. The purpose of morning cardio and evening Occlusion Training is to rapidly decrease serum levels of amino acids and glucose early in the day so that angiogenesis is magnified to the greatest extent in the evening hours post-exercise, this being a form of accelerated Methionine & Cysteine starvation, alongside a low level of hypoglycemia.

The following day(s) is / are your Strength-Refeed day(s), where you will consume large amounts of GlySer, slow and fast digesting protein, healthy carbohydrates, and essential fats, thus promoting the optimal Biosynthesis of tissue and energy stores. Even on a Pro-Cycle GlySer should be utilized on your Strength-Refeed days to reverse the process the catabolism, this will be a form of subtle *Rapid Inflammation Cycling* in relation to angiogenesis. If you skip your Strength workout, I suggest you not use any GlySer, as there is no point to increasing mTOR without destructive training, you'll only be aging yourself at that point.

Strength Training should be performed in the morning hours. The form of Strength Training you should utilize will be regular-speed tempo, as performing Extreme Tempo Training will delay muscle regeneration to too great of a degree. As for a specific Strength Training workout split, you should either; Train different muscle groups every Strength-Refeed day or train the same muscle groups and cycle between the use of partial repetitions to prevent prolonged overtraining.

Regarding Strength Training, do not be foolish and attempt to lift high loads with <u>full ROM</u> while fasting as that would be clearly counterintuitive to the primary goals of this protocol, as detailed in the Angio-Fast diagram I designed on the previous page.

If you wish to create balance between the muscle groups, every month or two consider changing your exercise scheme from lower body to upper body or vice versa, such that certain months you will be doing fasted cycling cardio and following day(s) refed bench press / row strength, while other months you will be doing fasted handcycling, boxing, or rowing cardio and following day(s) refed squat / deadlift strength. If reaching a balance between *Anabolism* and *Catabolism* is your desire, you should follow the LML Variation as it most closely aligns to an even split between fasting and refeeding, considering that we fast unconditionally when we sleep, a 24h Fasting / 48h Refeeding Split is as close to a biological balance as one can get.

As for proteolysis, because shorter duration fasting causes more muscle breakdown than longer duration due to the differences in ketone blood levels, and because exercising in a fasted state is liable to increase cortisol release, if you are deficient in muscle mass you should consume L-Ornithine on your fasting days and Potassium B-Hydroxybutyrate (+Sodium) to replenish one electrolyte and epigenetically counteract muscle atrophy (if your budget permits it). Proteolysis should generally not be of concern if you are

physically active, your training is intelligently programmed, and your refeeding days are composed of large amounts of protein and essential fats.

Do note that if you intend to follow this protocol while on an Anti-Inflammation Cycle, you should drink unsweetened Green Tea and take EGCg in the morning on your fasting days (before your cardiovascular exercise), this will enhance autophagy and amyloid clearance. Also, Occlusion Training should be removed from this protocol if you are on an Anti-Cycle, but you can replace it with Endurance Isometric Training, because this form of training is predominately slow twitch, and causes so little muscle damage, it can be added to any fasting protocol without risk of accelerated muscle atrophy, and is the safest and most intelligent way to lift "heavy" during periods of starvation.

If you are obese or focused purely on longevity and possess an adequate amount of muscle mass you should use the LLM Variation to maximally magnify autophagy thereby delaying aging to maximal extent.

Protocol Elaboration: If you're curious how it will be possible to *cycle* between anabolism and catabolism in such a short period of time, I will explain:
An increased intake of amino acids is only necessary to magnify early myogenesis in the proceeding 48-hours post-exercise, this parallels stem cell proliferation. If therefore you wish to engage in Angio-Fasting with the greatest forethought and efficacy, and you are using the MLL or LML Variations, you should place your heaviest workout, or the muscle groups you wish to grow to the greatest extent on the immediate day after your fast, to allow them adequate time to not only recover, but adapt, through high density macronutrient refeeding.

Protein powder combined with rapidly absorbable Essential Amino Acid powder (unflavored) are essential components of this protocol to promote hyperaminoacidemia following a fast, which when taken in the morning immediately before exercise will cause a massive surge in protein synthesis, a surge than can be used to promote hypertrophy following exercise. If you do not train early in the morning on your first or only refeeding day, or if you do not consume large amounts of fast digesting protein on this day, especially pre-workout, you will miss out on the aforementioned *anabolic surge*.

If you're following the LLM Variation, you should not lift too heavy, or train with too much volume on your Strength-Refeeding days for the clear reason that you will be depriving your regenerating muscles of necessary amino acids the following day.

Regarding Thermal Therapies, Hyperthermia Therapy should not be added to Angio-Fasting days even if it promotes autophagy or lipolysis, as similarly to Hypothermia Therapy it may disrupt or inhibit autophagy and stimulating an excessive amount of ROS which may damage cells components will only result in pathological autophagy. You should reserve your Thermal Therapies to the mornings or evenings on your Strength-Refeed days.
If you enjoy experimentation you could experiment with Hypothermic Angiogenic Sensitization in the evenings on your Refeeding days. [See: Pro-Inflammation Cycle Modalities].

If your legs become injured due to the chronic amount of cardiovascular exercise entailed in this protocol, and you are unable to use upper body cardio equipment, you

should halt your Angio-Fasting because fasting without exercise is in my opinion and based upon the previous research, *far too inefficient* at promoting autophagy alone. In the event that you become unable or unwilling to perform adequate amounts of cardiovascular exercise, you can always experiment with time-restricted eating (once a day), which is a safer form of fasting and best suited for beginners.

As with any cardiovascular-based workout protocol, you should always allot a month or two out of each year to solely strength train, ideally with ET:SS, your cardio-trained muscles, to renew and regrow the overtrained muscle tissue, if you do not frequently alternate between the upper / lower body cardio apparatuses.

If your ultimate goal is lipolysis and you wish to accelerate this process, remember that you absolutely must decrease your intake of carbohydrates and fatty acids on your refeeding days, fasting does not give you *metabolic merit* to overeat processed junk foods during refeeding. Conversely, if you do not consume an adequately large amount of macronutrients when you refeed, you may experience excessive autophagy, which will be detrimental to your health over time if unchecked, although it is quite clear that most citizens who reside within economically advanced nations do not suffer from excessive autophagy, they suffer from inefficient autophagy.

One may ask why angiogenesis is described as part of catabolism, and this is because I consider it an anabolic-catabolic compensatory process that exists in the biological milieu of cellular stress.

The intensity of the cardio prescribed is moderate, to moderate-high intensity, and this is to facilitate angiogenesis and neurogenesis in the brain, while also stimulating systemic autophagy. If you prefer lower intensity cardio you can always scale it back to 60-65% Max HR and double its duration to 120-minutes.

Finally, if you are extremely lean and do not possess a large amount of muscle mass, fasting-induced proteolysis becomes a dangerous variable, which is why you should reserve Angio-Fasting for periods wherein you have accrued a healthier amount of adipose tissue and a greater amount of muscle mass by following one of the previous strength protocols and eating normally. I do not mean to suggest fasting should only be reserved for those with expendable fat and muscle tissue as autophagy will still exert its antiaging effects on cells regardless of the two previously mentioned parameters, but you should save the most advanced Angio-Fast variation, LLM, for the periods of your life where you do possess catabolically expendable energy for the metabolism to utilize during starvation. The use of large dosages of BHB is one way to counteract proteolysis during Angio-Fasting, but this is only of necessity for use in those who do not possess sufficient amounts of muscle mass or adipose tissue.

Fasted exercise of all types will one day be commonplace in the fitness community and taught by numerous different types of health practitioners, that is after people finally begin to understand the dual beneficial differences between anabolic biological processes and catabolic biological processes.

Angio-Fast Variation *MLL*: Myogenesis > Lipolysis > Longevity

- Ω **Day One: Angio-Fast:** AM 70-Minutes of 70% Max Heart Rate Steady-State Cardio followed immediately by 5-Sets X 50-Seconds X 5-Minute Rest Periods Low Load Occlusion Training (or 2-Sets *IOT*).
- Ω **Day Two-Three-Four: Refeed:** AM Protein Shake followed by extended Exercise Warmups, then higher load resistance training. Refeed frequently with slow digesting carbohydrates, essential fats, & large amounts of high protein foods throughout the day.

Angio-Fast Variation *LML*: Lipolysis > Myogenesis > Longevity

- Ω **Day One: Angio-Fast:** AM 70-Minutes of 70% Max Heart Rate Steady-State Cardio followed immediately by 5-Sets X 50-Seconds X 5-Minute Rest Periods Low Load Occlusion Training (or 2-Sets *IOT*).
- Ω **Day Two-Three: Refeed:** AM Protein Shake followed by extended Exercise Warmups, then higher load resistance training. Refeed frequently with slow digesting carbohydrates, essential fats, & large amounts of high protein foods throughout the day.

Angio-Fast Variation *LLM*: Longevity > Lipolysis > Myogenesis

- Ω **Day One: Angio-Fast:** AM 70-Minutes of 70% Max Heart Rate Steady-State Cardio followed immediately by 5-Sets X 50-Seconds X 5-Minute Rest Periods Low Load Occlusion Training (or 2-Sets *IOT*).
- Ω **Day Two: Refeed:** AM Protein Shake followed by extended Exercise Warmups, then higher load resistance training. Refeed frequently with slow digesting carbohydrates, essential fats, & large amounts of high protein foods throughout the day.

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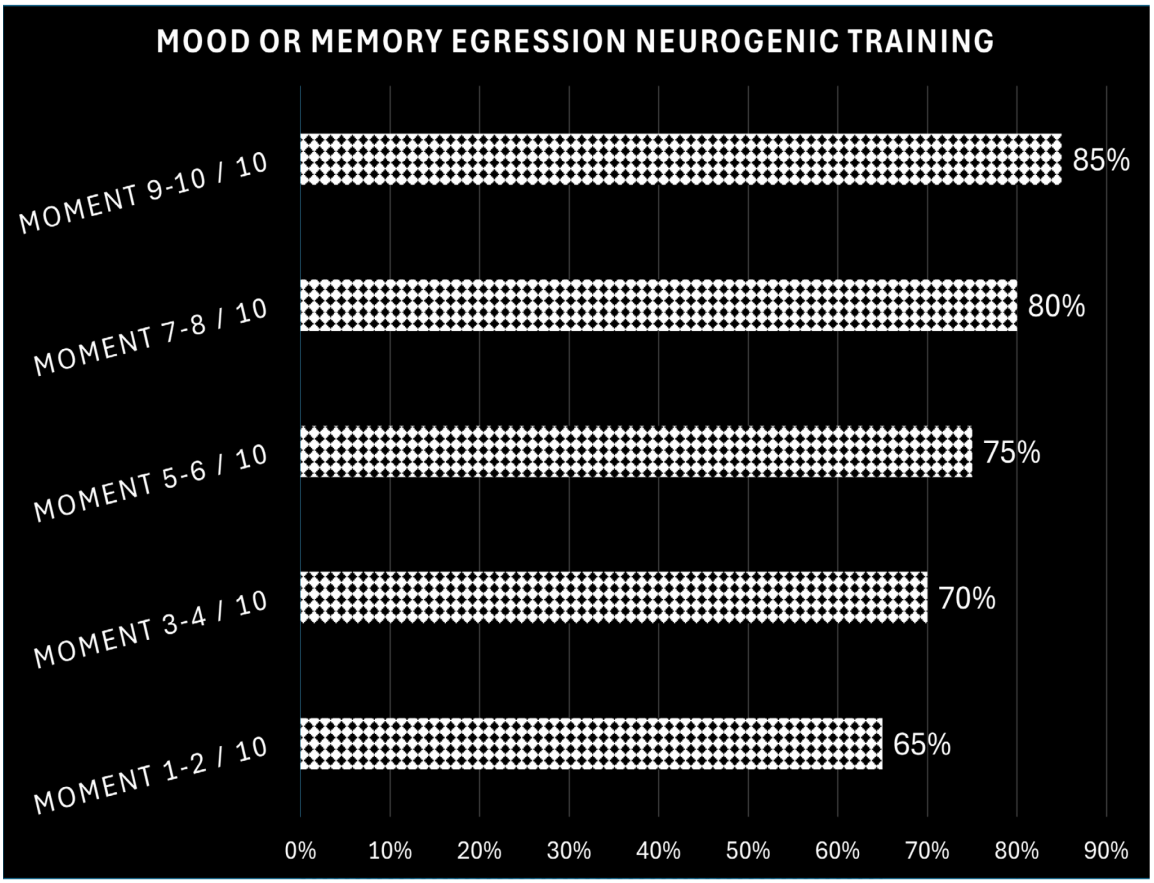
Mood Or Memory Egression Neurogenic Training © (MOMENT)



Protocol Background: Every *moment* in life matters, to appreciate life and to overcome its challenges requires optimally functioning cognitive abilities. Life becomes increasingly more difficult when Quantum Decoherence becomes dysregulated, but we can counteract this process through cardiovascular exercise. During periods of either psychological stress, or drug-induced neurotoxicity, such as with chronic caffeine, nicotine, THC, or alcohol use (withdrawal periods), it is of absolute necessity to increase not only the duration and frequency of weekly cardiovascular training, but moreso the intensity of the cardiovascular training performed, as this will protect, to a certain extent, your brain cells from excitotoxicity i.e. cell death. Although I do not believe RPE is an accurate measurement system of fatigue or effort, I do think its simplistic base methodology can be utilized to measure the progressive mood and memory egressions that begin to occur when under the influence of recreational drugs, or when exposed to psychological stress, hence my idea for MOMENT: The greater perceived mood or memory derangements you experience in a day, the greater intensity cardio you should perform (intensity as

measured by max heart rate percentages), to ensure adequate post-exercise bDNF release, to counteract the ongoing neurotoxicity, and to enhance inhibitory control.

In the chart on the previous page we see that for every subjectively-introspectively analyzed 20% deviation from your cognitive norm based on a scale of 1-10, with 0 to be considered a state of average emotional or cognitive function, 5% cardiovascular intensity is added incrementally, so that at your very worst—the times where you are severely depressed, stressed, or anxiogenic, or if your ability to form or recollect memories is significantly suppressed in the absence of changes to mood, you will engage in steady-state cardiovascular exercise at 85% your max heart rate (this would be MOMENT 9-10), until you experience a long lasting form of cognitive stabilization.

Protocol Background: Cardio should be performed two times a week for 85% days, three times a week for 80% days, four times a week for 75% days, five times a week for 70% days, and six times a week for 65% days. Every cardio session should be at or near to sixty minutes in length, this will allow ample time for the brain to be oxygenated through enhanced blood flow, saturated in lactic acid, and for the process of angiogenesis to occur within brain tissue (if you're on a Pro-Cycle).

Of course, it must be mentioned that firstly, this is a protocol for only the legs (not upper-body cardio), and secondarily, with greater intensity cardio, longer recovery periods are required, but in the case of protecting the brain from degradation, overtraining will be inevitable.

If possible, to avoid injury development, you should change your cardio exercise machine each workout, such as Stair Stepper > Incline Treadmill > Recumbent Bike.

This protocol will be especially valuable to those who suffer from environmental enrichment impoverishment, as the only nootropic of the poor man or woman aside from sociality, is exercise.

In my experience, you should not need to maintain higher MOMENT levels for more than a few months at a time, you should titrate down to lower MOMENT levels depending on how you feel at the start of each week, eventually returning to your entirely different chosen resistance training or cardiovascular exercise protocol after you feel you have reached an adequate state of cognitive stability or function (0-Baseline).

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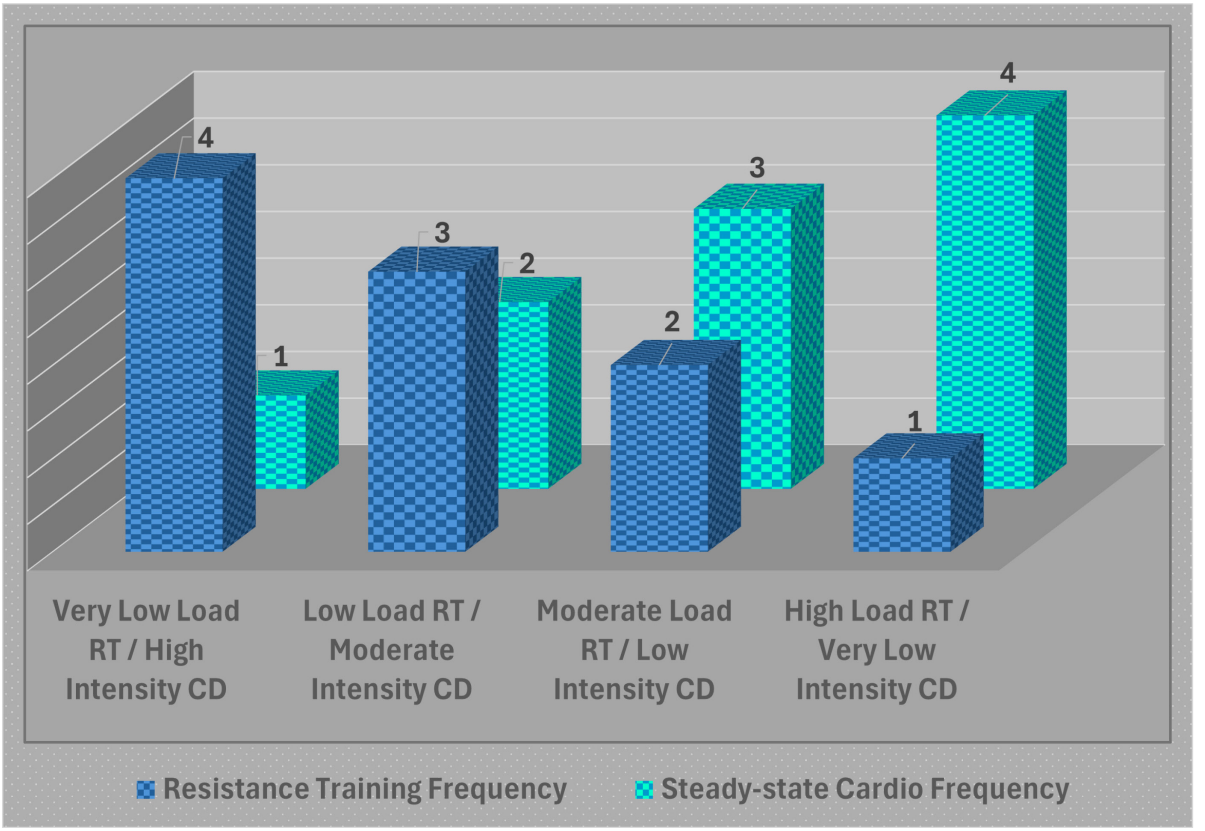
Inverse Correlation Exercise Protocol (ICE) ©



Protocol Background: In what regards strength training, because it is often complicated to plan detraining periods, and match them to overtraining periods, I have designed this *Inverse Correlation* exercise protocol, for those who wish to cycle between overtraining, optimal training, and what many would consider undertraining, with load / intensity-based detraining, alongside IMCycling, and Cardiovascular intensity cycling in the most intelligent way. This protocol follows linear periodization for loads and volume for resistance training, and reverse linear periodization for cardiovascular training intensity, such that you will be engaging in your highest frequency-lowest intensity cardiovascular exercise after your highest load-lowest volume resistance training session, thus promoting immunostimulation, while your highest intensity cardiovascular session will be performed on one day within your week of low load (immunoneutral) resistance training.

There will be an extremely low load (i.e. 2-3LB Dumbbells) Aerobic Resistance Training thorough warmup workout programmed at the final week on Friday (4-Days Post-Training), this will be to assure that muscle blood vessel density remains high, or at the very least does not drastically decrease through detraining-induced capillary

regression. This workout should be as low load as possible to safely promote hyperemia in muscles, tendons, and joints.
Now there are a few important points:

1. This workout protocol is extremely flexible and can be redesigned in just about any way possible, such that the IMCycling element can be removed entirely, the cardio percentages can be altered, or you can begin the protocol on a 5X a week split, if you like to live dangerously. You can also collate the daily workouts into solely AM, or solely PM training, but I believe the body and mind function most optimally with twice a day training.
2. This protocol requires the utilization of ARCS to function optimally, see the Cardio section for more information on this and other concepts.
3. The AM Warmups are vital to not only sensitize the muscles to be trained later in the day for anabolic growth, but also to prevent capillary regression, you can skip your high load training but do not skip these warmup workouts.
4. Stretching is not mandatory, but it is an excellent way to make your tendons pliable and injury resistant, and to grow a small amount of muscle tissue in discrete and highly sensitive regions of your body (shoulders, lower hamstrings, forearms), that is if you allow your body adequate time to regenerate itself, which is why you should absolutely not skip your detraining period after Extreme Stretching, and ensure that the weights you lift during your final bloodflow Aerobic workout are *extremely light* to efficiently deload and heal your injured muscles, tendons, and joints.
5. If you do not have access to Hyperthermia Therapy, Massage Therapy, or angiogenic supplements (Sildenafil / Nicotine), you should remove Week 4X (1) (X = Exercise Frequency) and begin at Week 3X (2), as it is my opinion that in the absence of stimulated angiogenesis, a very high frequency / high volume workout protocol becomes more destructive towards the musculoskeletal system. If you do remove Week 4X (1) then it makes no sense to keep Week 1X (4) considering that without overtraining, there is no point in slowly transitioning to undertraining. The same sort of logic goes for Week 1X (4) where you should be lifting high loads with far less volume. If you aren't consuming large amounts of dietary food protein, GlySer, protein powder, and anabolic nutrients, it does not make sense to lift too heavy as you may exceed your *stem cell potential for regeneration*.
6. Week 1X (4) is best suited for ET:SS owing to the extended detraining programmed, but you can train in any way that you so choose, as long as it is higher load, or moderate load with very high volume.
7. The "Overtraining" periods are programmed as lower load volume overtraining, or *angiogenic overtraining*, this is to reduce the risk of a serious injury occurring during training, but if you wish to lift heavy weight during your overtraining

weeks, consider partial ROM exercises, or utilizing gear (squat suit, bench suit, slingshot-like bench aid, or reverse heavy bands).

⅂ WEEK 1: 4X: PRO-CYCLE: ANGIOGENESIS: OVERTRAINING

MON/TUE/THU/FRI: RESISTANCE TRAINING: AM Fasted Thorough Warmups.
PM Very Low Load Lactic Acid Training or Very Low Load Occlusion Training.
WED: CARDIO: AM HIT Cardio 30min x 75%.
PM HIT Cardio 30min x 75%.

⅂ WEEK 2: 3X: PRO-CYCLE: ANGIOGENESIS: OVERTRAINING

MON/WED/FRI: RESISTANCE TRAINING: AM Fasted Thorough Warmups.
PM Low Load Lactic Acid Training / Occlusion Training.
TUE/THU: CARDIO: AM Fasted MIT Cardio 30min x 70%.
PM MIT Cardio 30min x 70%.

⅂ WEEK 3: 2X: ANTI-CYCLE: MYOGENESIS: OPTIMAL TRAINING

MON/THU: RESISTANCE TRAINING: AM Thorough Warmups.
PM Moderate Load Strength Training.
TUE/WED/FRI: CARDIO: AM LIT Cardio 30min x 65%.
PM LIT Cardio 30min x 65%.

⅂ WEEK 4: 1X: ANTI-CYCLE: MYOGENESIS: UNDERTRAINING

MON: RESISTANCE TRAINING: AM Thorough Warmups.
8:00PM High Load Strength Training.
TUE: AM 3h Extreme Stretching (for Resistance Trained muscles, or all muscles).
PM VLIT Cardio 30min x 60% Max HR.
WED/THU: CARDIO: AM LIT Cardio 30min x 60% Max HR.
PM VLIT Cardio 30min x 60% Max HR.
FRI: CARDIO: AM LIT Cardio 30min x 60% Max HR.
PM Anti-Capillary Regression Aerobic Thorough Resistance Training Warmups.

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Neural Efferent Unilateral Recruitment Aggregate Lability Protocol (NEURAL) ©

For those who find it difficult to facilitate or maintain a mind-muscle connection during a workout, or for those who grow tired of traditional compound lifts and symmetrical training, this a protocol for you. NEURAL is simply the act of training one side of your body within a 24-Hour period, allowing you to elicit greater neuromuscular junction changes post-training, due to increased intra-exercise focus and action potential signaling, and potentially, boosted motor memory strength, and maximal nerve conduction power to your isolated limbs. By separating, *generally, the right side of the body, by the left side of the body, especially regarding upper body exercises involving a gripping contraction, you should in hypothesis be able to isolate and activate different hemispheres of your brain, thus right arm exercises will preferentially stimulate left hemispheric cognition (analytical processing, motor memory), whereas left arm exercises will preferentially stimulate right hemispheric cognition (creative processing, spatial memory), meaning that after performing your Right-Side NEURAL Days you will be cognitively primed for analyzing and memorizing the world and its problems, whereas on your Left-Side NEURAL Days you will be cognitively primed for complex problem-solving, and artistic expression.

Beyond exercise, while following this chiral protocol, you should focus on switching dominant hands each day, for both mundane and for complex motor tasks such as using utensils when eating, picking up your cup, opening doors, to the more complex motor-intense acts such as writing, smartphone touch screen use, and brushing our teeth. This full day of hand-to-hemispheric switching will surely improve your intelligence over time.

Protocol Background: The first four weeks of this wide-reaching protocol involve alternating right and left side body training (depending on right / left hands), which will mean that you will be engaging in numerous different isolation exercises, invariably leading to greater muscle damage, which is why this is a protocol for alternating low-moderate loads only. There will be one washout week of bilateral compound training to restore motor memory, and mitigate any potential unforeseen musculoskeletal weaknesses that may develop from NEURAL Training, but this week is primarily to give your brain and body a respite from the difficulty entailed. You have the choice, as with any workout protocol I have formulated, to warmup in the morning, or immediately before your working sets (not recommended) with Thorough Warmups (Very Low Load Compound / Isolation Movements, No Restrictions), or ULTRAS (Low Intensity Lower Body Cardio + Arm, Shoulder, and Upper Back Aerobic Warmups), depending on which style of warmups you prefer.

One interesting thing you will notice on this protocol is referred pain or opposite side untrained muscle hyperemia, these are muscle sensations you will experience in the untrained side of your body, because the nerves that innervate each arm and leg converge in the spine, and because of the research mentioned before (Detraining, Deloading, & Vascular Deconditioning: [D]), it is plausible to suggest the possibility that you will accrue more bilateral (compound movement) exercise strength by following this protocol for a short period of time, considering that the nerves of each limb are linked, the greater transduction of force and effort in one limb may very well strengthen your motor memories and motor cortex efficiency beyond that of bilateral training. There must also be merit to my idea of 24h / 24h *Unilateral Cycling*, as this provides ample opportunity for motor memory consolidation, and exercise form mastery over time.

You may choose to fully incorporate Left and Right Side Days, and perform upper *and* lower body resistance training exercises for the matching limbs, but every workout protocol will benefit from the inclusion of cardio, most especially ARCS, and if you are crazy enough, you can choose to modify ARCS with Asymmetrical Training for the lower body muscle groups, such as by adding one ankle weight to your left or right ankles during treadmill or jogging steady-state cardio, cycling between lower limb asymmetries.

Regardless of the aforementioned thoughts, this form of training will at the very least improve angiogenesis and lactic acid generation in your isolated limbs considering the amount of rest periods you will take between each set will be shorter, and because of this I do not believe Occlusion Training is a necessary addition to NEURAL Training, as the time-under-tension, and effort will be far greater, leading to noticeable adaptations in muscle growth and conditioning. However, adding one or two short Occlusion Sets at the end of your NEURAL workouts will only result in magnified myogenesis.

Finally, an unforeseen benefit of what I term *Unilateral Cycling* is the time that will be spared each workout due to the shorter nature of the workouts to be performed, and less time required for effective targeted Myogenic Modality therapy post-exercise (as it is far easier to Vibrate the right arm and shoulder, than the right and left arm, selfsame to heat pad therapy, or deep tissue massage work), leading me to believe that this form of training is superior for those who do not have a limitless number of hours to train each day.

*Certain one handed exercises may activate the opposite side of the body, such as Right Handed Deadlifts resulting in left latissimus activation (as stabilizers). Regardless, on your Right-Hand Days, Right Handed Exercises are the focus.

[NRS] = NEURAL Right-Side of Body Training only
[NLS] = NEURAL Left-Side of Body Training only

<u>Week 1/3: NEURAL Training</u>

⌘ Day One / Four: AM [NRS] Thorough Warmups, or [NRS] ULTRAS.
PM [NRS] Low Load Lactic Acid Training.
Neuroplanning: Learning, Memorization, Productivity.
Right-Hand Dominant movements only.
Optional Right-Leg Weighted Steady-state Cardio.

⌘ Day Two / Five: AM [NLS] Thorough Warmups, or [NLS] ULTRAS.
PM [NLS] Moderate Load Reg-speed High Volume Resistance Training.
Neuroplanning: Problem-solving (Brainstorming).
Left-Hand Dominant movements only.
Optional Left-Leg Weighted Steady-state Cardio.

Week 2/4: NEURAL Training

⌘ Day One / Four: AM [NLS] Thorough Warmups, or [NLS] ULTRAS.
PM [NLS] Low Load Lactic Acid Training.
Neuroplanning: Problem-solving (Brainstorming).
Left-Hand Dominant movements only.
Optional Left-Leg Weighted Steady-state Cardio.

⌘ Day Two / Five: AM [NRS] Thorough Warmups, or [NRS] ULTRAS.
PM [NRS] Moderate Load Reg-speed High Volume Resistance Training.
Neuroplanning: Learning, Memorization, Productivity.
Right-Hand Dominant movements only.
Optional Right-Leg Weighted Steady-state Cardio.

Week 5: Bilateral Motor Memory Reset

⌘ Day One / Three / Five: AM Compound-only Full Body Thorough Warmups.
PM Compound-only Full Body Low Load Lactic Acid Training.
Optional Steady-state Cardio.

ENDURANCE NEURAL ULTRAS (ENU)

For those who are not afraid of pain and wish to extend their musclespan (the longevity of their muscles), I have created this NEURAL ULTRAS variation that accomplishes effectively the goal of upper body Endurance Training. While on a treadmill, hike, or recumbent bike, you will focus intensely on continuously performing one upper body isolation or semi-compound exercise for at or over sixty minutes, this will require a high pain tolerance and strong resolve, even if you use only 1LB Dumbbells (which is suggested).

These upper body Endurance Training sessions should not significantly impact your weekly training if you use loads that appropriate (1-2LB Dumbbells). ENU is an effective replacement for the aforementioned NEURAL protocol, as it can be performed in the morning as low intensity cardio, followed by thorough warmups, and evening bilateral, classical resistance training.

It must be mentioned that one should not focus heavily on maintaining a heart rate during ENU, as the primary goal is Endurance conditioning for an upper body muscle, or muscle group, therefore if you begin to lose upper body stability, such as while speedwalking, or rocking caused by intense recumbent bike cycling, and you lose your

ability to stabilize your left or right arm, and maintain adequate time-under-tension and contraction intelligence, you should decrease your lower body effort to facilitate upper body aerobic contractility.

I think it's a better idea to focus on only *One* upper body Endurance Exercise in the morning (per day), because sixty minutes is a long time, and it will cause a greater level of neural fatigue as compared to classic lower body-only Endurance Training. Finally, remember that ULTRAS is low intensity cardio, and you'll still need to incorporate morning or evening Moderate Intensity Cardio into any protocol, and you can add any upper body exercise to an ENU protocol such as the one below, just ensure it not drastically interfere with your walking stride, or seated cycling stability.

- ENU: Left Rowing,
- ENU: Right Rowing,
- ENU: Left Shoulder Pressing,
- ENU: Right Shoulder Pressing,
- ENU: Left Lateral Flies,
- ENU: Right Lateral Flies,
- ENU: Left Supinated Biceps Curls,
- ENU: Right Supinated Biceps Curls,
- ENU: Left Behind Head Triceps Extensions (Neutral),
- ENU: Right Behind Head Triceps Extensions (Neutral),
- ENU Left Shrugs,
- ENU: Right Shrugs,
- ENU: Left Neutral Biceps Curls
- ENU: Right Neutral Biceps Curls
- ENU: Left Wrist Curls
- ENU: Right Wrist Curls
- ENU: Left Reverse Wrist Curls
- ENU: Right Reverse Wrist Curls

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IMC Protocol Blueprints

(The included oral Cineole recommendations below are based on a non-toxic dosing plan only, consult with a licensed medical provider before experimentation)

LIPOLYTIC PROTOCOL BLUEPRINT:

Meal Supplements (each meal): Silymarin (AKT Suppressor), Alpha-lipoic acid (ROS / Caspase-3 Promoter), Conjugated Linoleic acid (Adipocyte Apoptosis), White Distilled Vinegar (Fatty Acid Oxidation), L-Carnitine (Fatty Acid Oxidation).

Workout Shake (Consume Half Pre-workout / Half Post-workout): L-Leucine (Slow-twitch Phenotypic Promoter), L-Serine (Stem Cell Promoter), L-Glutamine (IL-6 Promoter), L-Histidine (Neuronal Histamine), Agmatine (PGC1a Promoter), Piperine (AMPK Promoter), Potassium BHB (Ketones).

Dietary Fatty acids: Coconut-based MCT oil.

Permitted Seasonings / Sauces: Black Pepper, Sugar-free Hot Sauce (Low sodium).

Psychostimulant: Strong Coffee or Caffeine Pills consumed Pre / Intra-workout in morning every third day (two days washout period to retain lipolytic effect). Nicotine used in the 2-Day washout period for caffeine, or as the replacement for caffeine, but never use Nicotine for extended periods of time, no matter how physiologically healthy you feel.

Exercise Styles: Endurance Training, HIT Cardio, ULTRAS.

MYOGENIC PROTOCOL BLUEPRINT:

Myogenic Hydration Drink Choice A: Lime Juice (Flavor), Ascorbic Acid (Differentiation), Cineole (Antioxidant), Creatine (Differentiation), Agmatine (PGC1a Promoter).

Myogenic Hydration Drink Choice B: Safflower oil-free Unsweetened Coconut Milk (Calcium: Proliferation / Flavor), GlySer (Stem Cell Promoters), Creatine (Differentiation), Agmatine (PGC1a Promoter).

Morning Supps: Quercetin (Memory), Alpha GPC (Memory), Vitamin K1 (Proliferation), Vitamin K7 (Proliferation), Alpha Tocopherol (Antioxidant), Fish oil (Memory), DHEA (bDNF / NGF), Lactoferrin, Beta-Carotene (Memory), Liquid D3 (Immunostimulation), Jarrow B-Right (Metabolism / Memory), Lutein-Zeaxanthin (Antioxidant), Free Base L-Carnitine (Proliferation / Differentiation), Oleuropein (Antioxidant).

Meal Shake (each meal): GlySer (Stem Cell Promoter), Lion's Mane Powder (NGF Promoter), Beta-Alanine (MEF2 Promoter: Differentiation).

Workout Shake (Consume Half Pre-workout / Half Post-workout): Whey Isolate (Fast Twitch Phenotype), L-Histidine (Lipolysis / Proliferation), L-Ornithine (Cortisol Suppressor), Hyaluronic Acid (Joints), Taurine (Motor Memory), Chia Seed oil (Memory).

Dietary Fatty acids: Coconut oil (Fast Twitch Phenotype) + Grapeseed oil (Memory) + Polyphenol-rich EVOO (Antioxidant).

Evening Supps: Melatonin (Memory), Probiotics + Real-Sugar Meal (Immunostimulation).

TALM: Eucalyptus Globulus oil (Macrophage efficiency).

Aromatherapy: Cedarwood oil (CREB).

Psychostimulant: Camellia Sinensis Tea (Antioxidant).

Exercise Styles: ET:SS, Superslow Concentricity, Superslow Eccentricity, Regular-speed Resistance Training, Overtraining.

ANGIOGENIC PROTOCOL BLUEPRINT:

Angiogenic Hydration Drink Choice A: Lime Juice (Flavor), L-Glutamine (Angiogenesis), L-Ornithine (Cortisol Suppressor).

Angiogenic Hydration Drink Choice B: Echinacea Tea (Angiogenesis), L-Glutamine (Angiogenesis), L-Ornithine (Cortisol Suppressor).

Morning Supps: Sildenafil (Memory / Angiogenesis), Chelated Copper (Angiogenesis).

Workout Shake (Consume Half Pre-workout / Half Post-workout): L-Glutamine (Angiogenesis / Proliferation), Taurine (Angiogenesis, Motor Memory), L-Leucine (Slow Twitch Promotor).

Dietary Fatty acids: Sunflower oil (Angiogenesis).

Evening Supps: Melatonin (Neuroprotection), Bacillus Coagulans (IL-6 Promotor), Low Dose Alcohol Intra / Post-Workout (Angiogenesis).

Psychostimulant: Nicotine (LTP), or Sildenafil (Angiogenesis).

Exercise Styles: Occlusion Training, Lactic Acid Training, Endurance Training, Aerobics.

NEUROTROPHIC PROTOCOL BLUEPRINT:

Neurotrophic Hydration Drink: Lime Juice (Flavor), Ascorbic Acid (Antioxidant), Cineole (Antioxidant), Agmatine (Dendrite Arborization).

Fasted Morning Supps: Quercetin (bDNF / Anti-Dementia), EGCg (Neuroprotection / Anti-Dementia), DHEA (bDNF / NGF), Jarrow B-Right (Neuroprotection),

Morning Smoothie: L-Serine (Stem Cell Promoter), L-Theanine Capsule (bDNF), Chia seed oil (bDNF).

Meal Shake (each meal): L-Serine (Stem Cell Promoter), Lion's Mane Powder (NGF Promoter), L-Theanine Capsule (bDNF), Chia seed oil (bDNF).

Dietary Fatty acids: Grapeseed oil (Synaptic Maintenance) + Polyphenol-rich EVOO (Antioxidant).

Evening Supps: Chronic Melatonin (Neuroprotection), L-Theanine, Probiotics + Real-Sugar Meal (Extracellular Vesicles: Neuroprotection), Low Dose Alcohol (Cerebrospinal Fluid Promoter).

Bedtime Pillow Aromatherapy: Lavender Angustifolia oil (Anti-amyloid), East Indian Sandalwood oil (CNS Depressant).

Psychostimulant: Generic Green Tea (Catechins: Antioxidants).

Exercise Styles: Cardiovascular Exercise Specialization, Aerobic Resistance Training.

MYOGENIC DRINKS BLUEPRINT:

Variation Sour: Water, Creatine (Differentiation), Lemon Juice (Flavor), Ascorbic Acid (Differentiation).

Variation Sweet: Unsweetened Coconut Milk, GlySer (Stem Cell Proliferation), Creatine (Differentiation).

Exercise Types / Training Techniques

To alternate between all the variegated exercise types, training techniques, and exercise loads is not only interesting, but extremely healthy for developing a truly balanced muscle fiber typology, thorough intramuscular angiogenesis levels, and tendon strength.

I will say as before that Aerobic and / or low load Lactic Acid Warmups should be performed before every exercise session, but you should not combine too many exercise types in a workout, because you will likely overtrain, and also you will desensitize yourself to the joy inherent in changing how you train.

ET:SS Training should be performed to grow muscle tissue, whereas high volume, low-moderate load, regular-speed Classical Resistance Training should be considered Conditioning and incorporated into a training cycle to provide Myonuclei with longer lasting memories, to create a form of physical strength and hypertrophy that is resistant to detraining-induced losses, as Superslow Training and Powerlifting both are similar in that they do not result in long lasting increases in strength or power, only higher repetition, higher frequency training accomplishes this. You do not always need to combine Superslow Concentricity with Superslow Eccentricity, especially if you are an intermediate or expert lifter, although combing them makes training much more anabolic.

I am omitting detailing the training techniques, “Super Sets”, “Giant Sets”, “Drop Sets”, & “Cluster Sets”, because they are unintelligent and redundant training styles in my opinion. As an example, Super Sets are described as “performing two exercises back to back without rest”, but this training technique does not describe lactic acid, or tempo, or rep ranges. These training techniques are fun ways to engage in resistance training cardio, but one must remember that resting between sets will always build more muscle and neuromuscular prowess during classical strength training.

A. Aerobic Training is exercising a muscle with an extremely high number of repetitions measured not by number but by time (i.e. walking on a treadmill for an hour), it involves exercising with such a low load / resistance that no lactic acid forms in the muscles during exercise, this undoubtedly requires load below 3% your 1RM. This is the least anabolic type of exercise but simultaneously the safest.

B. Lactic Acid Training involves training a muscle with low-moderate loads (5-30%), but ideally lower loads (5-15%), and performing enough repetitions and maintaining enough time-under-tension each set to accumulate as much lactic acid within the muscles as possible. This form of training as be used as Exercise Warmups or it can have its own training day.

C. Superslow Concentricity Training is a type of training that isolates slow twitch fibers and is in my opinion much more exhausting to the CNS.

D. Superslow Eccentricity Training is a type of training that preferentially breaks down fast twitch and is therefore highly beneficial towards increasing absolute strength and muscle explosivity.

E. Explosive Training as covered previously is best used for two purposes, the first being to strengthen the CNS through high volume intervals, such as to imitate the exercise of sprinting, the second being to isolate and activate the fast twitch muscle fibers. Explosive Training is known in the lifting community as Speedwork, and it is usually performed with higher loads, very low repetitions, free weights, and large amounts of force, and for safer exercises and partial ROM movements I believe it is a safe form of training, but for bench press or rowing movements, it is dangerous to the soft tissue of the shoulders and arms, and I believe its effectiveness towards promoting absolute strength is overblown. A common misconception in the powerlifting community is that *you can only grow stronger or more powerful by lifting heavy weights*, but it is dangerous to teach individuals who do not have access to a myriad of anabolic steroids this, because it's a half-truth, as you can both strain and strengthen your CNS with light-moderate weight, as with heavy weight, and that is why I suggest using resistance bands and higher repetitions for all explosive workouts (such that if you were to do bench speedwork you would only use a barbell with band tension, not loaded), or if you intend on sticking with classical speedwork, stay away from exercises that involve a starting position ROM of a full stretch, and instead use partials (Box Squats, Board Presses, etc.). Explosive Training with high repetitions (HIIT Cardio) also has the benefit of promoting angiogenesis in fast twitch fibers. I do believe, in line with the research, that only HIIT Speedwork is capable of promoting adaptations to the neuromuscular junctions, meaning that although performing heavy explosive singles will be effective for growing fast twitch fibers, only performing sets of dozens of concurrent repetitions of explosive lifting such as to imitate the act of sprinting will lead to long lasting improvements to the mind-muscle connection.

Plyometrics are in my opinion silly explosive exercises that involve the use of interesting but unrelated exercises that are likely to have little carryover to physical sports. Classical Speedwork at the very least follows the law of sports specificity.

F: Isometric exercise is described as an exercise that involves no joint angle change. The primary types of Isometrics are:

- Isolation or Whole Body Classic Isometrics AKA Overcoming Isometrics (Unloaded): Applying an isolative or leaning concurrent force to an immovable object that is not heavy, such as a chain, bungee cord, strap.

Importantly, you are performing Classic Isometric exercise if you can move freely, there must be an immovable for you resisting.

- Overload Isometrics (an apropos term I coin): Maintaining a static contraction over constantly *changing* resistance with Bands, or Springs.
- Yielding Isometrics, or what I call Endurance Isometrics: Maintaining a static contraction against steady-weight over time.
- Shock Isometrics: Applying a leaning or side-stepping "hit" with high or near-max force to a chain or strap that ends in the generation of an upper body kinetic shockwave due to a sudden break in ROM. This is less similar to Compensatory Acceleration Training (Speedwork), but less dangerous.
- Enduro Isometrics (Endurance Overload): Maintaining an isometric hold while weight is continuously added incrementally, not progressively.

Isometrics are commonly suggested to be incorporated into a training cycle to treat "Sticking Points" in a lift, which I find to be ineffective, as in my humble opinion, they are best used as a way to train the CNS and muscles without the risk of overtraining or overt tendon damage. Although I suspect that training with any Static Holds will not improve your full ROM strength, Loaded or Unloaded Classic Isometrics may, as they recruit far more motor units, NMJ's, and stimulate the CNS to a greater extent during each set, but this does not make them the most effective option for surpassing Sticking Points, as this issue would more logically be treated through ET:SS Training, especially utilizing microreps.

Overload Isometrics can generally only be performed through locomotion, such that for armwrestling, you would take a resistance band, lock in a static joint position, and walk backwards or sideways until your muscles or tendons begin to tremble and fail, this is therefore a form of exercise only possible for upper body exercises, until new exercise equipment is invented. This form of Isometrics is much more tendon-based, as the loads change ever microsecond versus incrementally. Overload Isometrics were originally popularized by Travis Bagent as demonstrated in his years old Armwrestling seminars, and currently Mindaugas Tarasaitis uses this training style to maintain his world ranking spot.

Classic Isometrics can be performed as an isolation exercise, or whole body exercise, such that you may perform an overcoming isometric biceps curl focused solely on contracting the biceps, or you can maintain an isometric biceps joint angle hold and lean backwards while holding a stretched strap, or chain, or bungee cord, exerting far more force on your biceps, the former is more indicative of Superslow Concentricity Training, while the latter shares greater similarity to Eccentric Superslow Training as your joint angle will be opened slightly during whole body engagement, therefore leaning or step-

back Classic Isometrics are more damaging to the body (such as Max Load Lifting), whereas isolation isometrics are less damaging (such as Moderate Load Lifting). The primary benefit of performing whole body (leaning sideways, backwards, forwards) isometrics is the torso muscle recruitment that will come into play, resulting in your back and abdomen muscles becoming extremely strong, which is vital for Armwrestlers, and would surely be beneficial to powerlifters, and MMA athletes. Furthermore, I believe moderate load Endurance Isometric exercise is the very best training style for the elderly, and for females who do not possess dense musculature, considering their chance of injury is minimal.

H. Shock Isometrics is another form of Static Training that involves shocking the muscles, tendons, and joints through speed and impact shockwaves. Shock Isometrics are simply leaning or step-back Isometrics performed with *explosivity* and *impact*, and are to be considered an excellent joint, tendon, and bone conditioning exercise.

I: Resistance Endurance Training (RET) is simply my idea of targeted endurance training, wherein a muscle or muscle group will be trained for at or over 60-Minutes through concurrent concentric repetitions with commonly known resistance exercises, and not merely cardio machines (microreps), such that you will spend an hour doing supinated biceps curls with 1LB Dumbbells without rest, and with a relatively fast tempo. Although appearing seemingly useless to the average lifter and athlete, it serves the purpose of promoting isolated angiogenesis in slow twitch fibers, promoting hypertrophy without the need for heavier resistances, and facilitating ***Selective Autophagy***.

It is extremely important if you attempt this form of you training you use the lightest weight possible, that of which still allows you to feel a contraction, such as one pound dumbbells for biceps curls, or a children's barbell for bench press, for if you accumulate lactate in your muscles within the first ten minutes of constant contractions, or you have to rest due to an inability to contract due to Motor Unit Failure, you will need to lower the weight significantly. Even though Endurance Training a small muscle group may be time consuming and offer a rather unnoticeable reward it is an excellent way to condition a muscle and as aforementioned, to future proof it against expedited atrophy during periods of detraining, or even illness, and it is a safe way to rehabilitate an injured muscle, joint, or tendon.

Selective Autophagy is a term I use to describe endurance exercise that target specific muscle groups, or parts of a muscle, to stimulate the autophagic flux directly and locally, and selectively (remember GATA4?). There is undiscovered benefit to training a muscle group with greater ROM through RET beyond the greater spread of intramuscular angiogenesis (not the hyperlocal angiogenic patterning that occurs during cardiovascular

exercise microrepetitions), as it will delay the cellular senescence of your satellite cells. Do understand that performing sets of triples, sixes, or twelves will not delay the aging of your muscle tissue, unless you're on anabolic steroids, wherein cellular senescence is less of a threat due enhanced satellite cell production leading to stronger myonuclei memory. If you're a natural athlete, it is intelligence to embrace Endurance Training, even if you do so in short cycles.

J: Variable Resistance Training is both a new and old type of training style, it was first popularized in the powerlifting community by adding chains to compound barbell exercises. These chain links are attached to a barbell, where they descend and coil (unload) at the bottom of the bench press or squat ROM, and during flexion (lockout) the chain links are progressively lifted off the ground, thus adding "Variable" overload-like training intra-repetition.

Resistance Bands are another form of Variable Resistance Training that allow you to progressively overload a muscle group or your CNS, the elastic material increases in tension during stretching, thus too creating intra-repetition Variable resistance.

Adding Chains or Resistance Bands to a classic compound or isolation exercise generally makes that exercise safer, if they are used in place of increased loads, because the tension increases parallel to the ROM, peaking at or near the lockout position of the repetitions' range of motion, leading to less stress on the most sensitive parts of muscles and their tendons.

Variable Resistance Training can also be performed with industrial springs of varied tensions, and this is explained by Hooke's Law, which states that any force exerted by a mechanical spring is directly proportional to its displacement from its equilibrium starting position. The further the spring is displaced or stretched the greater force is required to continue to stretch or displace the spring, and therefore the greater force is placed on your muscles during a contraction. Training with springs is to be considered Overload Isometrics, which can be mimicked more simply with Resistance Bands, to do so simply buy a resistance band set online (the ones with handles) and attach them to the included door anchor in the top or bottom of a door, then begin by choosing an isometric joint position, walk backwards, or lean backwards, very slowly, progressively increasing the tension on your muscles and tendons, until you lose form.

K: Enduro (Endurance Overload) Isometric Training is a new type of training style and technique I conceptualized (but am surely not the first) that requires a second participant to load weights for you intra-workout. Instead of maintaining a certain load during each set of isometric exercise, you will use a plate loaded pulley machine, and every five, ten, twenty, thirty, or sixty seconds during active static holding your workout partner will add

a five, ten, or fifteen pound plate to the stack to increase the resistance steadily over time, until your starting ROM Point is lost completes, or it deviates beyond a certain percentage (5-30%) due to fatigue, or weakness.

L: Burnout Training is a form of a multi-set variable training that involves starting at a light weight, performing as many repetitions as possible (AMRAP) each set, and immediately after lactic acid or motor unit failure, adding a small percentage of weight, and performing another AMRAP set to failure, and continuing this until you've reached your 1RM, 3RM, or 5RM, then either stopping the session or performing a reverse burnout to maximal failure. Burnouts are best performed with machines as they allow one to quickly add weight each set. An ideal burnout would start at a low load, and progress each set to a maximal load, and last over twelve sets, for maximal blood flow and lactic acid accumulation.

M: Occlusion Training (Blood Flow Restriction / Kaatsu Training) is not necessary a form of exercise it is a method of training that is combined with a specialized type of exercise. Blood flow is occluded in the limbs intra-exercise to purposefully achieve muscle hypoxia, which causes cellular adaptation cascades leading to increased angiogenesis and enhanced stem cell proliferation.

N: Asymmetry Training is an excellent Exercise Technique to strengthen your core, or antagonist muscles during a lift, as through imbalance comes the activation of different muscle patterns. This type of technique may cause injury if the asymmetry between the left and right side are too severe, but this depends on the mind-muscle connectivity and motor intelligence of the lifter, regardless one should start with a small asymmetry weight difference of between 1 / 5, and progress over time to asymmetry ratios that are far higher, such as one-sided deadlifts (0 / 100), depending on their ability to maintain a smooth and balanced ROM, which may require a second participant or camera to tape and instruct their muscular imbalances.

O: Unilateral Training describes the act of using one limb at a time during an exercise, this Training Technique has the benefit of strengthening any weaknesses between each limb, or accumulating maximal lactic acid concentrations due to a far greater focused muscle contraction.

P: Friction Training is a future exercise type that I envision will replace superslow training in promoting unconventional strength gains. It will involve the use of novel exercise machines that offer a form of concurrent but uneven "gritty" resistance.

Exercise Types / Techniques Explanations

A. Aerobic Training: Explanation: Choose a load that is 1-3% your 1RM, perform hundreds upon hundreds of repetitions without rest or a change in form for sets of twenty, thirty, or sixty minutes. If lactic acid forms in the muscles or you experience motor unit failure during any point in time you must lower the weight you are using.

B. Lactic Acid Training: Explanation: Choose a load that is between 5-30% your 1RM, and with regular-speed or slower-speed tempo perform sets of over 30 Repetitions until you experience Lactic Acid Failure (Pain) and are forced to stop. If the exercise form you are using involves Quarter-Reps, you many reach Lactic Acid Failure after less repetition.

C. Extreme Tempo: Superslow Concentricity Training: Explanation: Starting from 0% ROM, move the weight as slowly as possible until 100% ROM, ideally between 8-12 Seconds time-under-tension. The muscle shortens during contraction.

D. Extreme Tempo: Superslow Eccentricity Training: Explanation: Starting from 100% ROM, lowering weight as slowly as possible to 0% ROM, ideally between 8-12 Seconds time-under-tension. The muscle lengthens during contraction.

E. Extreme Tempo: Explosive Training: Explanation: Starting at 0-25% ROM, contracting weight as quickly as possible with *higher repetitions, engaging the stretch reflex each repetition. The muscle shortens during contraction.
*Always use Resistance Bands and higher repetitions (HIIT) with Explosive Training as you will mitigate the risk for severe tendon, ligament, or joint injury and maximally train the Neuromuscular junctions.

F. Classic Isometric Training: Explanation: Find a ROM point between 1-99% and use a chain, strap, or bungee cord, or use any other immovable resistance to actively contract against such a squat rack safety stops. Contract against this immovable resistance for five to thirty seconds with maximal force, performing sets of many different ROM points. The muscle shortens during each set similarly to superslow concentricity, but this is not noticeable to the naked eye, Classic Isometrics should therefore be considered a form of *Microrepetition Concentric Superslow Training*.

You can perform Classic Isometrics Loaded (with weight) with a barbell, dumbbell, or cable machines, depending on if you have access to chains, a power rack with safety stops. Consider checking out the myriad of isometric bench, squat, deadlift, or Armwrestling (Todd Hutchings) exercise videos on YouTube for a better reference. There is an exercise device called the ISOCHAIN that is good for certain Classic Isometric exercises, although you can build something similar for a quarter of the price if

you have the time, or simply use a chain and your own body and train like Alexander Zass.

G. Endurance Isometric Training: Explanation: Hold a weight manageable weight in a certain ROM point between 1-99% ROM for between three to ten minutes, performing sets of many different ROM points. Endurance Isometric should be considered a form of *Microrepetition Endurance Training* and are likely to be the most angiogenic form of Isometric exercise, if lactic acid is generated during each set. You can make this form of training variable by using resistance bands, and every few minutes, before lactic acid failure, you can step closer to origin point of the resistance band, removing a small amount of tension on your muscles, to keep the muscle under tension, this Variable Endurance Isometric Training is wonderful for five to ten minute sets.

H. Shockwave Isometric Training: To train shock isometrics for the upper body, you take a short bungee cord, or a resistance band + chain, and either step back, step sideways, lean back, or lean sideways explosively while maintain an isometric hold so as to purposefully create a shockwave at the maximal stretching point of the bungee cord or the peak stretching point of chain, which will send this shockwave traversing through your joints, and if performed with enough volume should hypothetically increase the bone density of your arms and shoulders. For the lower body muscles, you can use an ankle harness and attach a carabiner and bungee cord to it, or a resistance band and chain, and perform any number of isolation leg exercises. This form of exercise comes primarily from the professional Armwrestler Todd Hutchings, who refers to this movement when paired with a cable pulley system and a chain as “Speedwork”, but it’s far more complex than speedwork. How you choose what angle to end your ROM is up to you, but in terms of isolation exercises it’s safer to find a ROM point where a muscle has reached the middle portion of the muscle belly, never near the lockout of the joint or muscle to avoid joint damage.

I. Resistance Endurance Training: Explanation: Endurance Training can be simplified as steady-state exercise performed for at or over sixty minutes, without rest, and most importantly without changing exercise form (if you do an hour of biceps curls, you must not change your wrist rotation or elbow position).

J. Variable Resistance Training: Explanation: This form of resistance training involves a special form of training wherein the tension or resistance experienced during an exercise either increases or decreases intra-repetition i.e. during the range of motion. This is best experienced through the use of Resistance Bands, or by using a traditional Rowing Machine (which severely overtrains the distal biceps muscles), wherein the tension either increases through the ROM or decreases through the ROM.

1. Chains: Attach powerlifting chains to your barbell or dumbbells, making it so the chain coils on the ground to lose a majority of its resistance during the starting point of the lift, or stretched phase of the exercises ROM.

2. Resistance Bands: Attach resistance bands to your barbell or dumbbells and follow the same idea as the use of chains, or use Resistance Bands with handles.

3. Overload Isometric Training (Springs / Bands): Attach a small mechanical spring to a wall mounted D-Ring or Eye Bolt with a carabiner and strap or chain, or use a resistance band with a door anchor. Through walking, or sidestepping backwards, or leaning sideways, apply enough steady and progressive force and stretch into the spring or band until either it reaches its maximal stretch point, or your muscles begin to fail, then walk or lean back to the starting point, and go again, or you can hold a static isometric contraction for a few seconds before resetting the tension. Ideally, you will perform "Pulses" of these Overload Isometrics, which equates to Overloading a muscle and joint to at or near its failure point, and then rapidly relieving tension, this will stimulate your fast twitch muscle fibers and allow you to accrue a large amount of muscle power in specific joint angles.

K. Overload Endurance Isometric Training: Explanation: Using a cable pulley system or an exercise apparatus that is plate loaded, find a suitable load to lift and ROM Point to train, begin your set, and every few seconds have your training partner add a certain number of pounds (barbell plates) to the exercise apparatus to progressively increase the force you are resisting until your muscles fail. The muscles lengthen during each set similarly to eccentricity, but this is generally not noticeable to the naked eye if form is adequately maintained, therefore this form of exercise could be considered a form of *Microrepetition Superslow Eccentricity Training*.

L. Burnout Training: Explanation: Start at a very a low load, and perform one AMRAP set to failure, then immediately add a small percentage of weight and perform another AMRAP set to failure, continue ascending in weight until you reach a high load where you can only perform a few repetitions with, and stop the exercise session here, or if you have the pain tolerance and willpower, begin descending weight with AMRAP sets to maximal failure. Do not follow any repetition scheme for this training style, train each set to failure.

M: Occlusion Training: There are two primary forms of Occlusion Training; Intermittent and Chronic. Intermittent Occlusion Training is the most common and well-studied, it involves occluding a certain percentage of blood flow in a muscle during a short duration high volume exercise set, following by long periods of reoxygenation (rest). There will

never be a perfect Occlusion Training protocol due to the complexities of and varieties of human muscle tissue, self-experimentation will be required to maximize its effectiveness.

N: Asymmetry Training (Offsets): Use a barbell offset by 1-100% (ideally 5-50%) during lower or upper body exercises, or use different weight dumbbells during lower or upper body exercises. Ensure that you maintain a level ROM, not tilted, or bent during the movement you may predispose yourself to injury.

O: Unilateral Training: Use a dumbbell, cable, or machine to exercise one arm, or one leg at a time, utilizing the extra flow of action potentials to better control the weight throughout the ROM, this being enhanced contractile precision, which benefits demanding exercises such as ET:SS, or LAT.

P: Friction Training: As of now there are no Friction exercise machines available, but I have plans to work with a metal fabrication specialist to design a new form of resistance training machine that will surpass superslow (concentric) training in efficacy. If you're interested in funding any of my mad ideas for exercise machines or future tech modalities, please email me dustin@inflammationcycling.com.

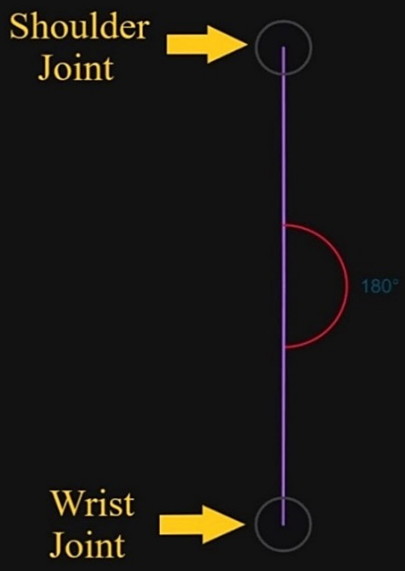
Exercise Range of Motion (ROM) Definitions

- Quarter-Reps are defined as 0-25% Range of Motion exercises i.e., starting from a fully stretched position to a slightly contracted (flexed) position.
- Middle-Reps are defined as 25-75% or 25-50% Range of Motion exercises.
- Partial-Reps are defined as 50-100% or 75-100% Range of Motion exercises.

I categorize all these ROM exercises as belonging to a class of ***Microrepetitions***. There are two subclasses of microrepetitions, muscle-specific and exercise-specific. Muscle specific microrepetitions are paired with isolation exercises, to train undeveloped parts of a muscle or ignore overdeveloped parts of a muscle.
Exercise-specific microrepetitions are often paired with compound or isolation exercises with the goal being to train weak or undeveloped parts of the muscle, but the primary benefit is preventing overtraining and reducing the risk of injury through allowing the most sensitive parts of a muscle, the muscle nearest to the insertion point versus origin point to rest by utilizing Partial-Reps. You will often encounter ignorant individuals misusing ROM terminology, suggesting for example that high squats (a squat performed without any depth) are “Quarter Squats”, which is nonsensical, the harder part of any exercise is the initiation of contraction from a stretched position, i.e. the 0-25% of the Range of Motion, therefore squats performed without “depth” are to be considered Partial Repetitions (50-100% - 75-100% ROM).
I believe ROM percentages or measurements should always be defined by the start of a repetition from a stretch / extension and then the end of a repetition with a contraction / flex.

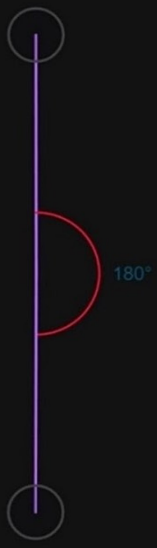
There is a great amount of projected insecurity in the fitness community and hate towards Partial-Repetition exercises, of Geared Lifting as it is called, but it is misguided. If a man adequately warms up every part of his upper body muscles with low loads, and dozens of exercises, and then lifts 1000lb’s with a bench shirt, he is not harming himself, and he may even be extending the longevity of his muscles and joints, for if one intends on training with high loads every single week, or twice a week, it is unsustainable to use full ROM exercises. That is not to say that there is not beautiful simplicity in lifting raw, but because most young individuals who obsess over absolute strength do not grasp the importance of detraining, deloading, and have been taught that overtraining is a myth, they progress at an accelerated rate towards the development of tendon ruptures, muscle tears, myogenic plateaus, and joint deterioration.

On the following page is IMC ROM Definitions demonstrated and visualized through the angle changes of different ROM Biceps curls (an isolation exercise).



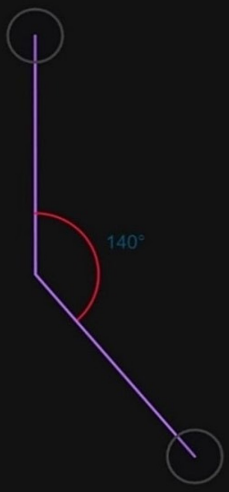
Biceps Curl
Full ROM Angles

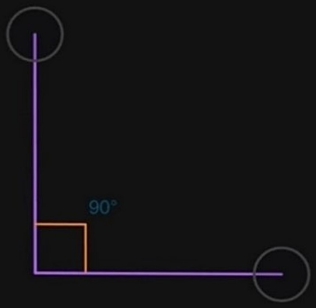
Start > End



Biceps Curl
Quarter Repetition
ROM Angles

Start > End





Biceps Curl
Partial Repetition
ROM Angles

Start > End

Visualizing the geometry of the three different primary types of Microrepetions for an Isolation Exercise such as the Biceps Curl in the previous image we see that at the bottom of the movement, the beginning of the movement, the biceps are stretched, they are at 0% ROM (extension) and the wrist joint is aligned to the shoulder joint at 180 Degrees, when they are fully contracted (flexed) they are at 100% ROM (flexion) and the two angle joints are nearly 20 Degrees apart, this is a Full ROM isolation exercise. When the Biceps Curl is started with the wrist at a 90 Degree angle, this is a partial ROM exercise (50-100% ROM). When the Biceps are completely extended and stretched with the wrist joint at 180 Degrees, and a very short contraction is performed, an angle change of around 40 Degrees, this is a 0-25% ROM exercise, a *Quarter-Repetition*.

In terms of compound microrepetitions, Bill Kazmaier was recorded bench pressing without lockouts (Quarter-Reps) in one of his oldest seminars uploaded to YouTube, and Benedikt Magnusson has discussed the importance of "Piston Squats", which are squats where you do not lockout, performed rapidly to maintain tension in the legs. Compound microrepetitions are excellent for powerlifters and bodybuilders, if the weights are moderate, and the volume is high, the lactic acid and blood flow that accompanies these sets is far more anabolic and therefore superior to regular-speed strength training, but obviously not ET:SS.

Depending the grip or stance, a compound movement Quarter, Middle, or Partial Rep may stimulate a large amount of muscle tissue, or target certain parts of muscle tissue, as an example if you perform a Quarter-Rep bench press AMRAP set with a wide grip you're clearing activating a very large amount of upper pectorals, and only a minor amount of triceps, whereas if you perform a Quarter-Rep bench press AMRAP set with a close grip, you're working a far more balanced split of muscle tissue (a large amount of triceps, and pectorals). It is generally not difficult to turn a compound lift into a near-isolation lift, such as Quarter-Rep squatting with your heels elevated and upper back arched, leading to the focused breakdown of the quadricep muscles.

Adding numerous low-load Quarter Repetition exercises to your workouts will result in the greatest amount of *noticeable* hypertrophy, because the part of the muscle that impresses us the most is the shape and size of the muscles that is nearest to the tendons, the stretched part of the muscles, not the fully flexed shape of it. Quarter Reps also build the most muscle during lactic acid training, because you don't lose "tension" on the muscles when you engage in limited range of motion, high volume exercise. Conversely, performing numerous high-load exercises that start from a stretched position will lead to the greatest chance of overtraining and muscle fiber destruction. High load Quarter Rep exercises risk damaging the joints and tendons when the loads lifted and volume are high, it is therefore intelligent to incorporate Geared Lifting into your workout protocol, as has been mentioned previously, to train heavy, at a high frequency, without a substantial risk of injury. The only problem with lifting more weight or training harder and longer with equipment is that for many individuals, a Partial ROM PR is equivalent to a Full ROM

PR, which is of course quite incorrect. If you do become too accustomed to Partial ROM exercises, you can always reset your motor memories and Ego by switching to a Full ROM Extreme Tempo Superslow Training protocol, putting great effort into moving the barbell as slowly as humanely possibly from the beginning of the repetitions ROM, at the stretched position.

A simple example of the pronounced hypertrophic effects of Quarter Reps: The individuals with the largest gastrocnemius muscles on the planet will always be morbidly obese persons, who train their calve muscles throughout the day with low loads by walking short distances. The greater the upper body mass present, the greater contraction is required during the stretched gastrocnemius ROM of the walking stride, leading to an extremely well developed and aesthetically impressive muscle being formed. Obese persons do not have large calves from doing full ROM calve extensions, or 1000lb calve extensions, they have large calves from unintentionally engaging in low load Quarter Rep repetitions through simply walking short distances each day.

Partial Repetitions are favored among powerlifters because they allow for the most impressive displays of physical power, as muscles contain more myofibers in the middle or higher portions of individual muscle groups, thus leading to greater force generation. Although training partial repetitions too often is a recipe for an Ego-induced musculoskeletal injury, they still serve a purpose, such as being a safe way to overtrain the CNS with high loads. There is also a valid argument for *Partial ROM Overload* to increase absolute strength, such as through the use of reduced ROM Exercises, or inclusion of Resistance Bands, or Chains.

Quarter Repetitions & Middle Repetitions are very good for rehabilitating damaged tendons, or damaged muscle tissue, and also they are necessary for to put the muscles under maximal time-under-tension, to accumulate the greatest amounts of lactic acid (Especially the Microrepetions of Cardio Training, which are in reality merely subsets of Quarter Reps), and blood flow during training. Both Bill Kazmaier & Benedikt Magnusson have discussed the use of “Piston Squats” in training, those being a form of high volume Middle Rep squatting that does not result in locking out the weight each repetition, allowing the tension to be maintained.

It's important to clarify that there is no wrong exercise, and most importantly you should not conflate full ROM exercises with “good / effective” exercises, and quarter or partial range of motion exercises as “bad / ineffective” exercises. Every exercise has a purpose, and playing with an exercises’ ROM is an intelligent way to isolate specific parts of a muscle to appear superficially larger and more intimidating or impressive, or to train longer and harder in a workout without an increased risk of injury. Just because an exercise activates more parts of a muscle, does not automatically make it an *effective exercise*, and this is why during warmups you should, and must perform many different exercises, and many different ROM’s for each exercise, to activate every part of every

muscle before an intense workout, for even if you have access to a children's barbell and can bench press 2.5lbs, 5lbs, or 10lbs with low loads before a heavy bench press day, you will still not be stimulating every part of your pectorals, triceps, and anterior deltoids, even by utilizing dozens of different bench press exercise variations, as you would still need to incorporate many different isolation exercises (with very load loads) to properly warmup, and because of the low loads required for optimal warmups, you will need to utilize quarter, middle, and partial repetitions to maintain *tension* and maximally accumulate both blood and lactate in your muscles, this means as an example to perfectly warmup your triceps before a heavy press workout you would want to perform very low dumbbell triceps extensions in the three primary ROM's techniques, and two or three different wrist positions (pronated, neutral, supinated), or for the chest; high-on chest pressing, low-on-chest pressing, wide-grip pressing, close-grip pressing, pronated / supinated pressing, et cetera.

As an example of the deleterious effects of being taught that only full ROM exercises are anabolic, and effective: The biceps are the most common "lagging" muscle group in resistance trainers, this is because they are consistently overtrained with high loads during back training, rowing exercises to be exact. The biceps brachii muscles do not respond well to this form of training because one does not often accumulate lactic acid in their biceps, nor blood, through high load rowing movements, also, considering most people train their biceps two, or three times a week, they provide very little time for their biceps brachii muscles to regenerate and adapt to the damaging exercises. A misinformed exercise guru may claim that we should outstretch our arms completely during any rowing exercise, to stimulate maximal upper back muscle growth, but this is not a wise thing to do, especially for natural athletes, as it is better to start most *higher load* rowing exercises at a bent-arm angle, which may only be possible for higher angle exercises, such as lat pulldowns, or pull-ups. By reducing the ROM of the biceps during high load rowing exercises, you will give the most sensitive distal parts of your biceps a chance to recover from exercises, or at the very least reduce your risk of overtraining-induced muscle atrophy, and injury.

It has taken me a great number of years to realize that full ROM exercises are best suited for very low volume high load training, or high volume low load training, especially in cases of stem cell impoverishment (natural lifting scenarios). The antagonist muscles of the biceps offer us a clearly definable dichotomy, for the triceps are rarely stretched during pressing movements, and are easier to hypertrophy, and they rarely become injured, clearly owing to the fact that they are not overtrained, or *stretched*, regularly. Do not therefore complain about having tiny biceps when you abuse them so greatly each week, they are very small and sensitive muscles after all.

Regarding ROM misinformation: Many ignorant gymgoers assume that Quarter Reps are "cheating", and they also will suggest that Box Squats, or High Squats are cheating, but they are confused. Quarter Rep exercises are harder, because of the increased need for

muscular stabilization, and the greater mind-muscle connection necessary for good form during high repetition sets. Partial Reps, such as the Box Squat or Board Press will always be easier exercises to perform, especially when the loads lifted are increased, because we are strongest at performing exercises that start with a ROM that begins with increased flexion and with joint angles that spread the tension across the most amount of muscle tissue, and we are weakest at performing exercises with a ROM that begins with increased extension, likely because there are more developed Neuromuscular Junctions in the middle part of our muscle bellies.

In Closing, we must remember that the human body was not designed to lift heavy weight, it was designed to lift light weight, this is why strength-endurance is easier to attain over absolute strength, that being muscle power. There should never be shame in performing altered ROM exercises, even though people will by sight alone consider you weaker for performing Partial ROM exercises, lower load Quarter Rep exercises, or IMC Warmups, and you may feel embarrassed, you must overcome your insecurities to become who you wish to be, whether that be healthy, strong, powerful, or physically-aesthetically pleasing.

It must also be mentioned that *Mastering* ROM changes can only be accomplished through low load training, as motor memories are not learned through short term straining, but through volume (repetition). Ensure therefore that you do not become slave to unspoken rules in your gym, which will or have already injured you in your naivety, and spend an adequately long period of time experimenting with all sorts of different exercise ROM percentage changes, such as Quarter Reps, Middle Reps, Partial Reps, and everything between. And as a final thought, it my general opinion that Partial ROM strength training is highly beneficial for the elderly, those who are physically weak, or the terminally busy, especially if they refuse to engage in low load training, because their chances of injury development is far less probable. If you are too busy in your day-to-day life to engage in thorough and extended IMC Warmups before a strength workout, you can always play with Partial ROM exercises, such as Partial ROM Overload Training, which will allow you to lift heavy weight in a safer way without the anabolic effects of pre-working set muscle hyperemia, and the high volume myogenic sensitization associated with warmup training.

ARCS, Cardio, Injuries, & Antagonist Muscle Activation

Alternating Resistance-Cardio Specialization (ARCS) ©

Scot Mendelson, a decorated Bench Press champion, who specializes in bench pressing, has said that he engages in recumbent bike cardio every day, and this led me to the conclusion that it is better to split up the muscle groups into Resistance Trained or Cardio Trained, to avoid injury and stay healthy. Focusing on one lift (Bench Press or Squat) is known as Specialization which you'll notice in my Workout Protocols.

The primary benefit of high frequency Steady-State Cardio at 60% Maximum Heart Rate is accelerating wound healing (of your resistance trained muscles, so long as you let them rest), but it is also the simplest way to promote synaptic plasticity. By following the

idea of what I call ***Alternating Resistance-Cardio Specialization*** **(ARCS)** you will gain the maximal musculoskeletal-neurological benefits from exercising. Let me be clear, ARCS may be explicitly understood as ONLY Strength Training one group of muscles while ONLY Cardio Training another *wholly separate* group of muscles, never combining them on a protocol i.e., Upper-Body Strength Focus / Lower-Body Cardio Focus.

It may seem strange at first to separate the body by upper and lower body muscles by strength trained, and cardio trained, but you will find that it is one of the very best ways to structure training, considering cardio should never be neglected, and any overuse injuries developed through high volume cardio training will only be magnified through high load resistance training, for to squat heavy one day and then perform hours of cardio in the following days will eliminate the anabolic benefits of optimal detraining and perturb myogenesis within the leg muscles. Also, because Muscle Memory exists, there is really no point in obsessing over the maintenance and growth of every compound lifts' absolute strength simultaneously, unless competition is your passion. It is far better for your mind and body to cycle between upper and lower body strength and cardio specialization.

If you only train your muscles with light weights (below 30% 1RM), or if you are on a strict Occlusion Training protocol then ARCS really has no place in your life, considering you will be recovering speedily from your resistance training workouts, and training a muscle multiple times a week with both lower load, fuller ROM resistance training, and microrepetition cardio training will not significantly affect your progress in the gym, but for those who prefer to lift heavy weights, and are not solely focused on skeletal muscle conditioning (angiogenesis), ARCS will be necessary to reach your immunological and myogenic potential.

High Intensity Steady-state Cardio (Concurrent, not Intervals, 30-60 Minutes) at 80-95% your Maximum Heart Rate is an important form of cardiovascular exercise for specifically the brain and heart, but also the neuromuscular junctions, but selfsame to higher load resistance training, it will require greater recovery time, and thus should be only performed once every week or two to avoid prolonged immunodepression, or injury.

Injuries

If you find yourself with a severe or chronic muscle, tendon, or ligament injury, firstly you should engage in daily resistance training specific aerobics (1-2% 1RM) to promote blood flow and angiogenesis in the damaged tissue, and twice weekly Lactic Acid Training, or Occlusion Training, until most of the pain and weakness has dissipated, and then if the muscle or tendon is capable of being stretched, begin an extreme stretch protocol, ideally once a week for an hour or more.

Secondly, for muscle injuries, schedule weekly Deep-Tissue Massages (or Active Release Technique sessions), once the area is healed of course. I suggest that the massage

therapist use their elbows or another similarly sharp but rounded tool during the massage, and that they use a great amount of pressure during each vertical or horizontal stroke, to break up any scar tissue. Penetrating and painful massage is also beneficial for tendon regeneration, from my subjective experience, as at one point in my life, after pushing my car on a dirt road to imitate my favorite strongmen, my Achilles tendons became heavily injured at the insertion points. I had a friend use the end of a gripper (Captains of Crush) to massage with great force the tendons at the lower insertion points in the heel, and they healed well, although it was quite painful.

Finally, in my opinion the other way to rebuild or grow your tendons is through Superslow Concentricity resistance training, I would not exceed 30% your concentric 1RM, but you must give your tendons ample recovery time, especially if they are injured, ideally two weeks between sessions.

I must mention a vital and often neglected point to consider when you experience a subtle and manageable injury, such as tendonitis, or localized muscle soreness (not DOMS), just because you are no longer sore does not mean you are not still injured, or that your injury has healed, and you have developed a near-permanent weakness in your musculoskeletal system. Small injuries often predate the development of large injuries, it essential to continue the rehabilitation therapies and training adjustments you made at the earliest stage of injury rehab, for months after the injury has seemingly recovered.

Antagonist Muscle Activation

Research has shown that during free weight Bench Pressing or Lat Pulldowns, antagonistic muscles are always activated. This means that when you Bench Press, your Biceps are activated, and when you Lat Pulldown (Row), your Pectorals are activated, making it essential that you warmup both the targeted muscles and the antagonist muscles before each workout, to avoid unintended overtraining. The Golden Era of bodybuilders unconsciously understood this and performed “Supersets” of opposing muscle groups.

[A] Wider-grip bench pressing results in greater biceps activation, likely due to the increased need for stabilization.

“<>Background: This study compared the muscle activity and six repetition maximum (6-RM) loads in bench press with narrow, medium, and wide grip widths with sub-group comparisons of resistance-trained (RT) and novice-trained (NT) men.
<>Methods: After two familiarization sessions, twenty-eight subjects lifted their 6-RM loads with the different grip widths with measurement of electromyographic activity.
<>Results: Biceps brachii activity increased with increasing grip width, whereas wide grip displayed lower triceps brachii activation than medium and narrow. In the anterior deltoid, greater activity was observed using a medium compared to narrow grip. Similar muscle activities were observed between the grip widths for the other muscles. For the

RT group, greater biceps brachii activity with increasing grip width was observed, but only greater activity was observed in the NT group between narrow and wide. Comparing wide and medium grip width, the RT group showed lower triceps activation using a wide grip, whereas the NT group showed lower anterior deltoid activation using a narrow compared to medium grip. Both groups demonstrated lower 6-RM loads using a narrow grip compared to the other grips.
<>Conclusion: Grip widths affect both 6-RM loads and triceps brachii, biceps brachii, and anterior deltoid activity especially between wide and narrow grip widths."[537.0]

[A2] Dumbbell Presses activate the biceps.

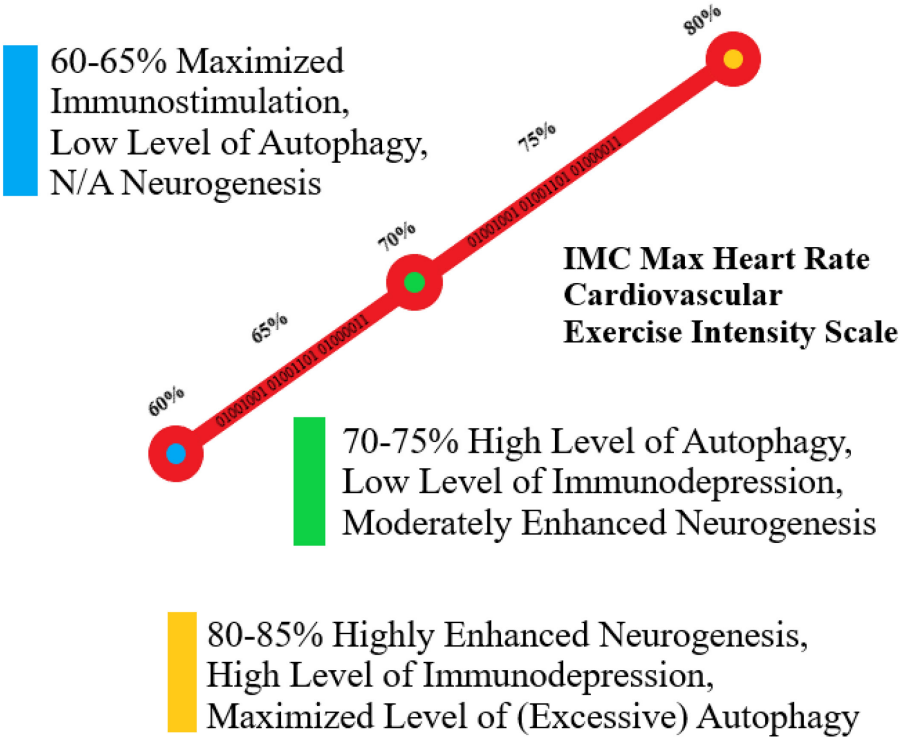
"<>The purpose of the study was to compare the muscle activity in the prime movers and antagonist between the barbell bench press (BBP) and the dumbbell flyes (DF) Seventeen resistance-trained men (age 22.9 ± 1.8 yrs; height 1.80 ± 0.06 m; body mass 80.0 ± 8.3 kg), with 4.8 ± 2.0 years resistance training experience, completed the study. The surface electromyographic activation was measured in four different muscles (pectoralis major, anterior deltoids, triceps brachii, and biceps brachii) during six repetition maximum loads in both exercises. To better understand eventual differences, an in-depth analysis of the fifth repetition was performed, dividing it into six phases (lower, middle, and upper phase of the descending and ascending movement).
<>The results showed a higher muscle activation in the whole movement and the majority of the lifting phases for pectoralis major, deltoids anterior, and triceps brachii for the BBP compared to the DF (8-81 %, $p \leq 0.05$). However, the antagonist biceps brachii showed a higher muscle activation (57-86 %, $p \leq 0.05$) in the DF compared to the BBP.
<>In conclusion, both exercises could be included in training programs, but the BBP should be emphasized because of the higher muscle activation overall. Among specific populations, were tasks based on strength and control in a horizontal shoulder flexion position with extended elbows often occurs, the DF might prove useful."[537]

[B] Lat-Pulldowns activate the pectoralis muscles.

"<>The purpose of this work was to evaluate the activity of the primary motor muscles during the performance of 3 lat pull-down techniques through surface electromyography (EMG). Twenty-four trained adult men performed 5 repetitions of behind-the-neck (BNL), front-of-the-neck (FNL), and V-bar exercises at 80% of 1 repetition maximum. For each technique, the root mean square from the EMG signal was registered from the pectoralis major (PM), latissimus dorsi (LD), posterior deltoid (PD), and biceps brachii (BB) and further normalized in respect to that which presented the highest value of all the techniques. A series of two-way repeated measures analysis of variance was used to compare the results, with Tukey-Kramer as the post hoc test and alpha = 0.05.

<>During the concentric phase, PM value showed the FNL to be significantly higher than V-bar/BNL and V-bar higher than BNL. During the eccentric phase, FNL/V-bar was higher than BNL. For LD, there was no difference between techniques. PD presented BNL higher than FNL/V-bar and FNL higher than V-bar in the concentric phase and BNL higher than V-bar in the eccentric phase. BB exhibited BNL higher than V-bar/FNL and V-bar higher than FNL in both concentric and eccentric phases. Considering the main objectives of lat pull-down, we concluded that FNL is the better choice, whereas BNL is not a good lat pull-down technique and should be avoided. V-bar could be used as an alternative."[538]

Cardiovascular Exercise


60-65% Maximized Immunostimulation, Low Level of Autophagy, N/A Neurogenesis
60%
65%
70%
75%
80%
IMC Max Heart Rate Cardiovascular Exercise Intensity Scale
70-75% High Level of Autophagy, Low Level of Immunodepression, Moderately Enhanced Neurogenesis
80-85% Highly Enhanced Neurogenesis, High Level of Immunodepression, Maximized Level of (Excessive) Autophagy

Steady-State Cardio (SSC) should be performed at 60-65% Maximal Heart Rate (MHR) to accelerate muscle regeneration [A]. Any Cardio session performed at MHR percentages higher than 70-75% will benefit the brain and cardiovascular system more than the entire body and musculature by promoting neurogenesis [B] at the cost of *slightly* delayed wound healing through immune system stress. This does not mean that all cardio should be performed at or near 60-65% your Max Heart Rate, it means that 70-75% Max Heart Rate Steady-state Cardiovascular exercise should be performed less often, depending on current health metrics, and intelligence, ideally a minimum of two times a week for its neurotrophic benefits, whereas for those who are currently healthy,

and content with their mental fitness, 60-65% for 60-120 Minutes in the morning during the workweek is sufficient for the promotion of general health. Unfortunately, it is likely that you will underestimate your MHR, therefore it is better to hover between 65% or a point or two higher most low intensity cardio days to ensure you do not drop below the low intensity threshold.

The total minimum duration of cardio required to promote systemic health, or neurological performance does depend on intensity in my experience. Workouts below 60-Minutes for 60% LIT Cardio will be insufficient to promote *maximized* immunostimulation, whereas workouts below 30-Minutes for 70-75% will be insufficient to promote *noticeable* cognitive improvements. Many elderly individuals go on short walks every day, and although this may be good for them, it is not enough volume, therefore if you or a loved one is to walk at a slow pace on an even surface and maintain a sub 60% Max Heart Rate, you or your loved one should walk for not merely twenty or thirty minutes per day as doctors and fitness magazines suggest, but instead for multiple hours (2-4) per day to elicit statistically significant systemic cellular effects.

Engaging in SSC workouts is a wonderful time to learn, by playing an informative podcast or audio book, as it will enhance memory encoding [C].

It is a misconception spread in the fitness community, mostly by bodybuilders and powerlifters, who say confidently that cardio is the enemy of systemic muscle growth, but this is just not true, as it truly depends on the intensity of the cardio performed, not the volume therein. High intensity cardio may be more anabolic, locally, in cardio-trained muscles, due to the increased breakdown of fast twitch fibers and the greater accumulation of lactate, but it is also immunosuppressive, similarly to high load resistance training, therefore the old saying that “cardio burns muscle” is only partially true, as low intensity cardio will not burn non-cardio trained muscles, nor should it interfere with myogenesis. It is true however that prolonged cardio, of any intensity, without adequate fuel (carbohydrates, amino acids, potentially fatty acids), may very well result in the perturbation of non-cardio trained muscles’ myogenic propensity, such as if blood glucose levels fall too low, or if AMPK rises to too great of a level, but this is easily counteracted through the consumption of pre/intra-workout protein and carbohydrates, especially GlySer, to suppress AMPK. I do not believe that even three hours of low intensity (60%) steady-state cardio will interrupt hypertrophy or hyperplasia processes in other muscle groups, and this training may even accelerate these processes through immunostimulation, but to be safe the best option on a strictly anabolic protocol is to never go over an hour of cardio without adequate intra-workout fuel (carbs, amino acids).

I believe low intensity cardio should be performed four to six days per week, whereas two or three of these LIT workouts should be replaced with moderate or high intensity cardio depending on your current health metrics; the more cognitive or health issues you suffer from, the more moderate-high intensity cardio sessions per week you require.

The greater the amount of fat you carry, the greater the intensity and duration of cardio you will require to remain physiologically and neurologically healthy, due to the stress placed on the heart, the potential insulin sensitivity loss, and the increased basal level of inflammation, so do make sure to increase your low intensity, moderate intensity, and high intensity cardio percentage by around 7%, thus if your Max Heart Rate is 180BPM, and you are unwillingly obese or on an extended Adipocycle, and you choose 65% Max HR as your low intensity cardio, your workout would be performed at 125BPM versus 117BPM.

[A] "<>Moderate-intensity aerobic exercise has been noted to improve wound healing rates in mice and people, but different intensities of exercise may have different impacts on healing rates. It is important to determine the most beneficial exercise intensity for improving wound healing in people with type 2 diabetes to help prevent wounds from becoming chronic, greatly reduce pain and immobility, and lower the high cost of health care associated with treatment.
<>Objective. The purpose of this study is to determine the impact of low-intensity exercise compared with high-intensity exercise in terms of the rate of wound healing in diabetic mice. Materials and Methods. Twenty-one 10-week-old female diabetic mice were randomly assigned to a sedentary control group (CON), low-intensity treadmill exercise (LEX) group, or high-intensity treadmill exercise (HEX) group. Mice were exercised for 30 minutes, 5 days per week, for 3 weeks. Mice were wounded on their upper back with a 3.5-mm punch biopsy instrument, and wounds were photographed at the same time every day.
<>Results. In terms of the length of time it took wounds to fully heal, CON mice healed in an average of 14.4 ± 2.4 days (number of days to decrease to less than 10% of their original size ± standard deviation) and HEX mice in 14.0 ± 3.0 days (P = .396). However, LEX mice healed faster than CON in an average of 10.1 ± 2.3 days (P = .004).
<>Conclusions. In this preliminary investigation, low-intensity exercise accelerated wound healing rates in diabetic mice, but high-intensity exercise did not. Future studies should investigate the mechanisms behind this effect and evaluate different intensities of exercise on wound healing in humans with type 2 diabetes.
<>Exercise protocol. Exercise was performed on a modified Jog-A-Dog adapted with lanes for individual mice with protective pads placed on the back of each lane to prevent injury. No electric shock or any other kind of stimulus was used in this study. Low-intensity exercise was performed at 12 meters per minute on a 5% incline while high-intensity was at 18 meters per minute on a 5% incline. This represents about 60% and 85% of maximal capacity for these mice at 10 weeks of age (data unpublished). Mice were exercised for 30 minutes, 5 days per week, for 3 weeks."[539]

[B] High Intensity Cardio increases bDNF expression, as the intensity increases, bDNF expression increases. Although this study suggests that bDNF increases to a greater extent after interval training, this is due to the intensity differences, not the duration.

"<>Exercise can have a positive effect on the brain by activating brain-derived neurotrophic factor (BDNF)-related processes. In healthy humans there appears to be a linear relationship between exercise intensity and the positive short-term effect of acute exercise on BDNF levels (i.e., the highest BDNF levels are reported after high-intensity exercise protocols). Here we performed two experiments to test the effectiveness of two high-intensity exercise protocols, both known to improve cardiovascular health, to determine whether they have a similar efficacy in affecting BDNF levels.
<>Participants performed a continuous exercise (CON) protocol at 70% of maximal work rate and a high-intensity interval-training (HIT) protocol at 90% of maximal work rate for periods of 1 min alternating with 1 min of rest (both protocols lasted 20 min). We observed similar BDNF kinetics in both protocols, with maximal BDNF concentrations being reached toward the end of training (experiment 1). We then showed that both exercise protocols significantly increase BDNF levels compared with a rest condition (CON $P = 0.04$; HIT $P < 0.001$), with HIT reaching higher BDNF levels than CON ($P = 0.035$) (experiment 2).
<>These results suggest that shorter bouts of high intensity exercise are slightly more effective than continuous high-intensity exercise for elevating serum BDNF. Additionally, 73% of the participants preferred the HIT protocol ($P = 0.02$). Therefore, we suggest that the HIT protocol might represent an effective and preferred intervention for elevating BDNF levels and potentially promoting brain health."[539.A]

[C] Instead of listening to music during your Steady-state Cardio, consider listening to an informative audio book, to improve memory encoding. You would be surprised how much you can learn while moving your body.

"<>Moderate physical activity improves various cognitive functions, particularly when it is applied simultaneously to the cognitive task. In two psychoneuroendocrinological within-subject experiments, we investigated whether very low-intensity motor activity, i.e., walking, during foreign-language vocabulary encoding improves subsequent recall compared to encoding during physical rest. >Furthermore, we examined the kinetics of brain-derived neurotrophic factor (BDNF) in serum and salivary cortisol. Previous research has associated both substances with memory performance.
<>In both experiments, subjects performed better when they were motorically active during encoding compared to being sedentary. BDNF in serum was unrelated to memory performance. In contrast we found a positive correlation between salivary cortisol concentration and the number of correctly recalled items. In summary, even very light physical activity during encoding is beneficial for subsequent recall."[539.B]

Continuous BPM Monitoring

Being able to actively record your BPM (Heart Rate) during a workout is quite revolutionary, but when following BPM-focused protocols, looking at your wrist every five to ten seconds to ensure you are within a certain BPM Range is quite uncomfortable, and the use of most heart rate applications with IMC workout protocols is not feasible due to the inherent lack of training options, where only classical heart rate zone training is permitted. The best way to fix this issue, if using my preferred heart rate monitoring technology, the Apple Watch, is through the Apple Watch Mirroring setting in the iPhone, or through the use of a third-party application such as Heart Graph, or Cardiogram.

If your eyes are not constantly watching your BPM during a Steady-state cardio workout, and you are not consistently making tempo, contraction intensity, or resistance adjustments during your training, you will surely deviate from the workout protocol, by ramping up or dropping off from the programmed BPM Ranges unintentionally. Interval Training does not often require you to monitor your heart rate, because there is really no point in keeping track of these workouts, as they depend far more on muscle conditioning rather than cardiovascular conditioning, and although it is far easier to engage in Unconscious Cardio, by walking on a treadmill, or by cycling at a comfortable speed, without paying any mind to track your BPM, this is no longer a suitable way to train, unless you lack the necessary heart rate monitoring technology.

Although many treadmills and exercise bikes come installed with integrated heart-rate monitors (sensors) in their handlebars, maintaining a grip on these heart rate monitors is an unnecessary inconvenience in my opinion, considering that as you maintain your grip, you must also maintain a comfortable body position that allows that specified kinesiological grip position, such as an arched back, slouched back, or retracted / protracted elbows. The use of these integrated heart rate monitoring technologies while engaging in long duration cardiovascular exercise only add an unnecessary motor difficulty to each session. Furthermore, in the cases of treadmill integrated heart rate sensors, the forced pronated grip will quite possibly strain your shoulders, or biceps, if you do not walk fast enough, and end up having these handlebars tug your upper body during each stride, as I see far too often women and men being tugged by treadmills, exerting unintentional torque to their arms and shoulders, and this is a natural and unconscious way to make the cardio easier I would suppose. Because of this, if the only option is the use of an integrated heart rate monitor, one should attempt to only hold the handlebars on a treadmill very lightly, with little or no tension on the fingers, to avoid inadvertently damaging the arms or shoulders during exercise.

Diet-induced Heart Rate & Muscle Exertion Differences

When the muscles have reduced glucose availability, their absolute and top-end power (not endurance) will drop off to an unknown extent, possibly by 5-15%. This is of course due to the exhaustion of glycolytic muscle fibers. So too will the cardiovascular system be weakened, not through damage, but reduced energy availability. Although a person's low intensity cardiovascular threshold of failure may increase on a carbohydrate-restricted diet, their high intensity cardiovascular threshold of failure will decrease noticeably, due again to a decrease in fast twitch fiber fueling and function. Although high intensity cardio while glycogen depleted, or under low blood glucose level conditions will increase the difficulty of said workout tremendously, due to increased lactic acid generation, and accelerated motor unit fatigue, these will be necessary difficulties to overcome to maximally accelerate lipolysis, or promote rapid lactic acid-induced neurogenesis following HIT Cardio. While in the cases where your mind and body are in good health, it would be wise to save your highest intensity cardiovascular workouts for dietary periods wherein you consume far more carbohydrates—where your fast twitch muscle fibers are fueled properly pre, intra, and post-workout.

An Introduction to Endurance Training: Fat Percentage-based Cardio (FPC)

One of my ideas, although experimental, is to define lower body steady-state cardio (SSC) intensity by fat percentage, and to simultaneously provide a simplistic introductory Every-Other-Day (EOD) (Detraining two days a week, or four days every three weeks) cardio protocol for those who are either overweight, seeking maximal leanness, or wish to improve their cardiovascular health. FPC is designed specifically for those who either despise cardio, but adore strength training, or have no experience in Endurance Training. It is a periodized / reverse-periodized cardio protocol to aid individuals in reaching their lipolytic and fitness goals (when combined with a strict diet). It is simple to understand, and unlike my cardio specialization workout protocols, the duration of each workout within each Segment does not increase or decrease, leading to a better ability to plan workouts, and less physiological stress.

Considering that Endurance Training is intimidating or too difficult for most, this protocol has been separated into three-three month segments, each with four repeating Body Fat % Subsets (+30, 20-30, 10-20, & -10) cardio recommendations, to condition the brain and body slowly, with Segment-3 being the ideal protocol to maintain until either:

A. An optimal fat percentage has been reached, wherein the participant will switch back to their chosen cardio protocol.

Or

B. The participant feels confident and conditioned enough both mentally and physically to embrace a serious cardio specialization protocol of greater intensity and / or volume, for lipolytic or longevity purposes.

Or

C. The participant enjoys the neurotrophic and health benefits of Endurance Training and maintains Segment-3, and regarding the use of FPC for fat loss, possibly begins experimenting with AdipoCycling for the promotion of myogenesis in their ARCS strength trained muscles, switching between Segment-3 Subsets yearly, depending on accrued fat percentages.

Segment-1: Months 1-3: Introductory FPC: EOD Training

+30% BF = 1H X 69% MAX HR SSC
+20-30% BF = 1H X 66% MAX HR SSC
10-20% BF = 1H X 63% MAX HR SSC
-10% BF = 1H X 60% MAX HR SSC

Segment-2: Months 3-6: Intermediate FPC: EOD Training

+30% BF= 2H X 69% MAX HR SSC
+20-30% BF = 2H X 66% MAX HR SSC
10-20% BF = 2H X 63% MAX HR SSC
-10% BF = 2H X 60% MAX HR SSC

Segment-3: Months 6-?: Optimal FPC: EOD Training

+30% BF = 3H X 69% MAX HR SSC
+20-30% BF = 3H X 66% MAX HR SSC
10-20% BF = 3H X 63% MAX HR SSC
-10% BF = 3H X 60% MAX HR SSC

In terms of Segment-2/3, although the volume may seem severe, when multiple cardio apparatuses are used in a day (Treadmill, Recumbent Bike, Stair Stepper), the difficulty becomes far easier due to the differential activation and spread of muscle fatigue. As an example of the protocol in action: If you are above 30% body fat, you would begin with Segment-1: 1-Hour x 69% Max Heart Rate, and in three months move to Segment-2: 2-Hours x 69% Max Heart Rate, and finally to Segment-3: 3-Hours x 69% Max Heart Rate where you will maintain the programmed Endurance Training.

Considering those who are obese tend to possess greater amounts of muscle mass, and possibly, when facilitated through cardio, a greater ability to hypertrophy due to adipokine-angiogenesis differences, the intensity scale decreases depending on total body fat.

Because it is assumed a person will be on diet during the use of this protocol, it is a mistake to engage in frequent high intensity cardio without greater detraining periods, this is therefore a temporary workout protocol.

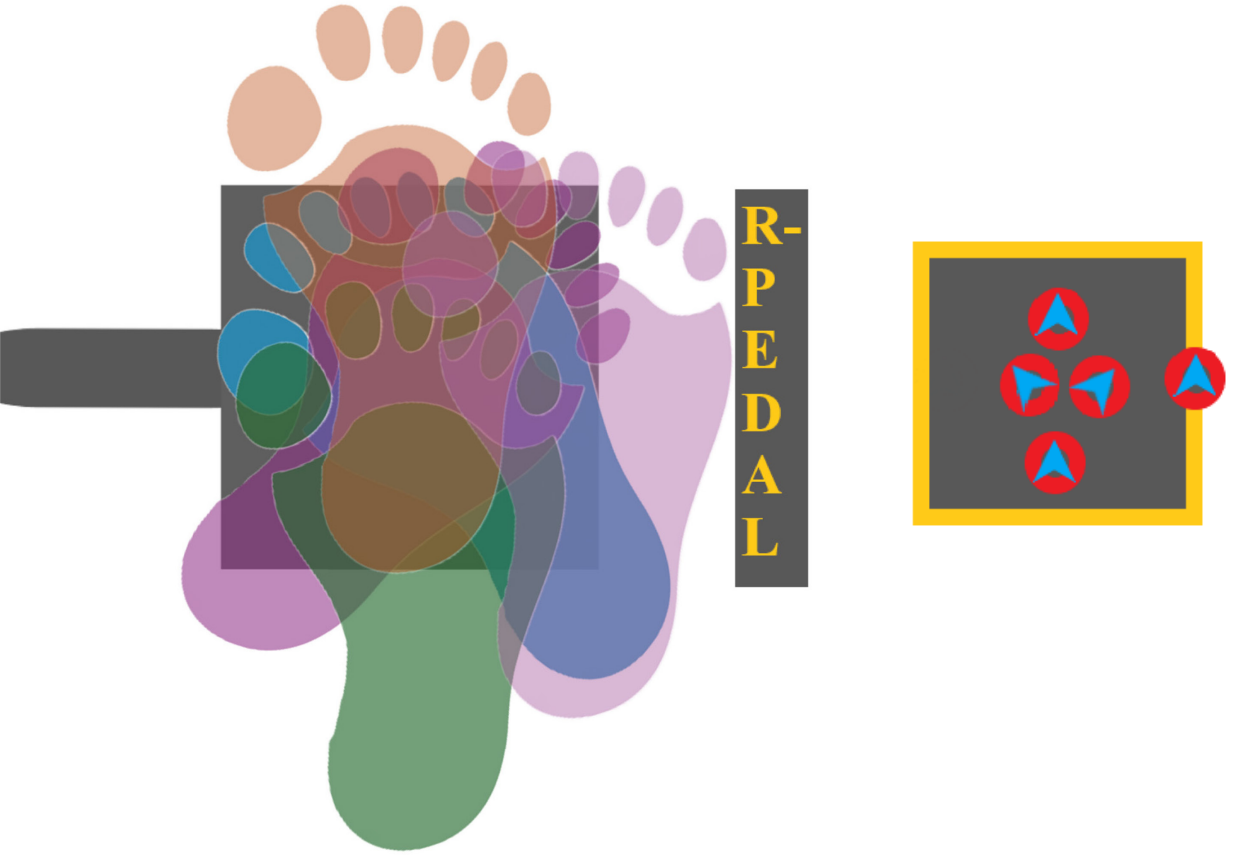
Though you are likely to burn fat in Segment-1/2, depending on the severity of your diet, and will quite possibly reach your targeted body fat percentage over a longer period of time, you should still work towards Segment-3 to not only expedite the process of lipolysis, but also to promote neuroprotection, and potentially (depending on intensity) neurogenesis and neuronal angiogenesis, and of course longevity through immunomodulation.

Equilibrious Dynamic Intermittent Form Intra-Cardio Exercise (EDIFICE) ©

When I do any form of low intensity cardio, every two-six minutes, I change my exercise form, to activate different and obscure parts of my cardio-trained muscles, to create a balance in muscle conditioning and development, I refer to this technique as *EDIFICE*. You may be thinking to yourself "What do you mean change exercise form during cardiovascular exercise? There's only one way to walk, or bicycle!" and you'd be wrong in this assumption, as there are dozens of large or small adjustments you can make regarding foot position, foot angle, and seat height during lower body cardio exercises, selfsame to upper body cardio, see the examples below:

Treadmill EDIFICE: Walk with an arched back, Walk with a stooped gait, Walk with your toes pointed out, Walk with your toes pointed forward, Walk with a static bend in your knees, Walk with a large amount of torso rotation, Walk in smaller steps, Walk in larger steps, Walk with a greater Q-Factor (distance between heels), Walk on your tippy toes, Walk on your heels. (Always try to use a Treadmill with a 22" Running Belt, or greater in width, as any other size is inferior for EDIFICE)

Recumbent Bike EDIFICE: Cycle with your toes pointed in, Cycle with your toes pointed out, Cycle with pressure on your heels (high foot position), Cycle with pressure on the ball of your foot (low foot position), Cycle with an open groin (+ feet pointed out), Cycle on the edge of the pedals (vertical wide stance), Cycle with a slouched back, Cycle with an arched back, Cycle with static plantarflexion, Cycle with the maximal static dorsiflexion, Cycle with a high seat position, Cycle with a low seat position. (Many of these variables are dependent on the use of a recumbent bike, which offers more kinesiological leg and foot position flexibility to play with intra-exercise due to the position and angle of the seat in relation to the crankshaft, and many of these variations in form (foot position) require pedals that are wide width, and ones that have removable straps, which you will remove during exercise).



All of the previous cardio exercise-specific variations in form will activate different parts, or entirely different muscles, in your lower body muscle chain during exercise. For pure cardio, or competition, locking your feet into position through the use of clipless pedals or a strap is great, but for the sake of preventing injury, and growing your muscles in subtle but balanced ways, you should and must incorporate my idea of EDIFICE, especially for cardiovascular exercise equipment training, as you will mitigate the development of overuse injuries. As a reminder of form specific muscle activation, the primary Hamstring muscles, the Semitendinosus & Semimembranosus, are activated more through a Pronated Foot Position (Toes-pointed in), whereas the Biceps Femoris are activated more through a Supinated Foot Position (Toes-pointed out). And regarding the Gastrocnemius muscles; The Lateral Head is activated more through a Supinated Foot Position, whereas the Medial Head is activated more through a bent-knee Pronated Foot Position.

EDIFICE involves the act of rapidly changing your exercise form *intra-exercise*, and if you are strong and have developed nearly every muscle in your body it should not significantly change your BPM output during steady-state cardio, unless you have muscle weaknesses, which will surely be rectified after a few weeks of EDIFICE Training, but

most importantly, if you are at risk of falling due to age or neurological condition, you should stick with recumbent bikes only.

Please understand EDIFICE is designed for pairing with Low Intensity SS-Cardio Training, 60-65% Max HR. It makes no sense to rapidly change your exercise form when engaging in dangerous HIT / HIIT Cardio, that of which is dependent on constant and predictable kinesiological stability.

Importantly, EDIFICE must be performed *consciously*, you must attempt to activate and contract every muscle in your cardio-trained muscle chain with each pedal stroke, or step; The glutes, hams, quads, calves. You must do this with focus on unilateral contraction, and therefore begin to consider cardio exercise as microrepetions of unilateral contraction, rather than Unconscious Exercise where the rhythm of contraction prevents the activation of the entire muscle chain. When you cycle, consider it a Unilateral Leg Press, or Leg Curl, et cetera. You can zone out and train Unconsciously for the majority of your low intensity cardio workouts, but for the purposes of conditioning the various parts of each hamstring, gastrocnemius, or quadricep, you must pay more mind to how you move, even if it requires a greater expenditure of neuronal energy.

Finally, EDIFICE can and should clearly be incorporated into upper body cardio workouts, such as rowing with a pronated grip—a supinated grip—a neutral grip, rowing with an arched back—a slouched back, rowing at a high angle (towards the neck or face)—rowing at a low angle (towards the stomach), and rowing with your elbows out and in (trapezius versus rhomboid focus). It is so strange to me that I have never seen anyone in my local gym rowing with a supinated grip, maybe one day this will change, or so the short heads of their biceps wish.

Cardio Addendum A: If you own your own Bicycle, or Exercise Bike, make sure to install 27mm pedal extenders on the crank arms of your bike to enhance the width between your heels during each pedal stroke, this is called the “Q-Factor”, and it will permanently reduce a small amount of stress placed on your hamstrings and meniscuses intra-exercise. It doesn’t matter how narrow your hips are, everybody will benefit from a shoulder width or wider squat stance, especially with high volume exercise, and yes, bicycling is merely microrepetition squats.

Cardio Addendum B: In terms of Treadmill and Hiking exercise, it is an excellent idea, for a short period of time, to add Heel Lift’s to your shoes to change the muscle activation during each stride. This idea may seem a bit flamboyant, especially for a male, but it’s a good way to add variation to any walking (not jogging, running, or sprinting) exercise protocol to target the calves, glutes, and hamstrings in a novel way. Consider how Tom Platz, the man with the most impressive legs in history, would squat with specialty powerlifter shoes, those that have a raised heel, which when combined with a high bar barbell position, allowed him greater depth and vertical form during his squat

ROM, to target the lowest, and most impressive when hypertrophied parts of his quadriceps muscles.

Cardio Addendum C1: Weight vests are a good alternative way to train in various lower-end BPM Ranges for those who despise fast paced leg locomotion (running / jogging), but it must be mentioned that the lower hamstrings are overtrained often, and very similarly to the biceps in that regard, and if possible it is more intelligent to use a Recumbent Bicycle, or Stair Stepper cardio apparatus for cardio training, as these exercise machine choices will spread the tension of your bodyweight across far more leg muscles, beyond the lowest points and most sensitive points of the posterior chain. Also, it is far better kinesiologically that is you train on a treadmill, you always do so with a slight incline, this will ensure that your stride is more balanced, leading to less strain on your hamstrings and greater gastrocnemius activation.

Cardio Addendum C2: The previous information, being directly correlated, now brings up the argument that although running cardio is supremely healthy for the heart and mind, and is most impressive, as it is a bodyweight exercise that can be performed nearly anywhere, and for free, this form of exercise isolates and damages to a large extent the hamstrings and meniscuses during movement, which will often lead to a subtle or overt injury developing, most especially if you specialize in this form of exercise, and train it three or more times a week. If therefore you have weak and small leg muscles, you should follow in the suggestion in Addendum C1, to avoid overtraining and injuring yourself, but if you have well developed and strong hamstrings grown from intelligently programmed bodybuilding or powerlifting workouts that have properly utilized detraining periods, I see no major risk with maintaining a running-only cardio protocol.

Interestingly, I personally believe, leaving aside alcohol and NSAID use, that hamstring and meniscus injuries develop most often in those who jog or run predominately on flat surfaces such as roads and sidewalks, because these surfaces almost always have a slight slope to them, often unnoticeable to the uninitiated eye, and because the routes runners (joggers) take do not often involve backtracking, and if they do backtrack they do not remain on the *same exact side of the path they started on*, the slope is never reversed but instead only mirrored, thus overtraining one leg in the process. If you prefer running on flat surfaces, ensure that you return exactly the same way you came, on the same side of the sidewalk or street, to allow the subtle slope to train your other leg equally, even if that means running towards traffic, or against it, or towards pedestrians, however rude or strange that may seem.

Of note, traditional hiking is the greatest example of natural EDIFICE, where the leg muscles, especially the calves and hamstrings, are trained through numerous different

angles, and forced foot position changes, due to the rocky and uneven terrain, thus strengthening any weak points in the aforementioned tissue.

Posterior-Anterior Central Nervous System Training (PACT) ©

I have found it necessary to separate upper and lower body cardiovascular exercises into two parts, which may be useful for those who are specialized in Endurance Training, general fitness, or on a weight loss protocol:

- **Morning Posterior Cardio:** Incline Treadmill, Legs-only Elliptical, Rowing Machine, 1" Battle Ropes, Rowing-only Sci-Fit, + unmentioned Hamstring-Calve / Rowing Muscles Dominant Cardio.
- **Evening Anterior Cardio:** Stair Stepper, Recumbent Bike, Standing-in-place Boxing, Wall-ball Throws, Pressing-only Sci-Fit, + unmentioned Quad / Pressing Muscles Dominant Cardio.

The primary reason for this body split is that I find it is more difficult to perform Anterior-based cardiovascular exercise in the morning when I am not fully awake, as Posterior-based cardiovascular exercises tend to utilize less muscle, and therefore require less neuronal excitation to actuate, and considering in general it can be said that our hamstrings-calves and biceps-rear delts are more conditioned that our quadriceps / abs and front delts / pectorals, there will be in general less Central Nervous System fatigue and stress that results after Posterior-based cardio workouts, which is why in my ideal world, the morning would be reserved for Posterior-based cardiovascular exercises, and the evening for Anterior-based.

One may ask why both the Recumbent Bike, and Stair Stepper would be considered "Anterior" exercises, the reason for this is that these two exercises tend to activate far more of the quadriceps than Walking – Jogging – Running, meaning that you can and should differentiate them from the former exercises. Of course, if you do not maintain some degree of purposeful Plantarflexion during your Recumbent Bike cycling workout, you may just end up isolating your hamstrings, which is why if you follow in line with this type of training you ensure that you maintain a plantarflexed calve position to target your quadriceps during any Recumbent Bike sessions.

If you experiment with PAC, you should find that you are not as tired later in the day, although this may be only subjective, I do find there is logic in this form of training. As an extra piece of information for you, in terms of utilizing Battle Ropes for cardio, to avoid overtraining the biceps, you should attempt to use a *one inch* diameter rope, and tape some Fat Gripz handles to them to engage more forearm and hand muscles during exercise.

Unilateral Locomotive Tapered Regenerative Aerobic Steady-state Training (ULTRAS) ©

In scenarios where an individual prefers maximal exercise time efficiency, *ULTRAS* training offers the opportunity to hypertrophy multiple upper body muscle groups within short periods of time, while simultaneously improving systemic cellular health through low-moderate intensity cardio. Quite simply, ULTRAS is walking-hiking (and wintertime recumbent bike cycling) at a steady-pace, while performing upper body unilateral dumbbell resistance training aerobics, such as curls, lateral flies, overhead triceps extensions, shoulder pressing, wrist curls, et cetera. Although it may seem difficult to perform arm exercises while engaging in low intensity Steady-state lower body cardio, it is entirely possible, and quite addictive when mastered. Hike & Curl is the simplest and easiest to perform example of ULTRAS, but there are many more unilateral exercises to perform while engaging in lower body cardio and upper body aerobics, ones that require greater coordination and a better mind-muscle connection. Because ULTRAS involves for the most part, cycling between many different upper body exercises, your BPM is liable to spike or drop rapidly, and this makes ULTRAS cardio a form of low intensity Interval Training, therefore do not attempt to maintain a heart rate zone (BPM Range) while experimenting with this form of training, unless you allow a 10-15 point BPM range of deviation. You can of course specialize in one upper body exercise during ULTRAS exercise, such as biceps curls, or shoulder presses, and work towards conditioning a specific group of muscles, potentially promoting Selective Autophagy, and this would allow you hypothetically to maintain a stricter average BPM.

The ultimate goal of ULTRAS cardio is to *gently* hypertrophy, condition, and regenerate upper body muscles through moderate-high volume Aerobics, while improving systemic immunity, there is therefore absolutely no reason to lift more than a 1LB dumbbell if you're a man, and 1/2LB microplate if you're an unfit woman, or elderly man during your workouts, for if you accumulate lactic acid in your upper body muscles, you'll be defeating the purpose of the training, and confusing your muscles.

ULTRAS is an excellent way to perform both muscle and Neurogenic warmups in time-restricted scenarios, such as Treadmill-Triceps Ext-Shoulder Pressing before a strength press workout, although obviously it will never be a complete nor perfect warmup workout.

ULTRAS upper body aerobics should and must be performed with static antagonist muscle activation in your body, most especially the upper back muscles to maintain time-under-tension and avoid explosivity contractions, you should perform no more than two repetitions per second to achieve this, if you are unable to maintain upper back tightness while simultaneously focusing on a smooth walking or cycling stride during your ULTRAS training you should not pursue this method as you will only injure yourself.

Finally, ULTRAS should be performed outside, in green areas, such as hiking, to attain the benefits of VOC exposure, sunlight, and to experience a reprieve from artificial

electromagnetic waves. You should find your training to be meditative, and if you find it boring you can always play an audio book or podcast to keep your mind preoccupied, but do ensure that you do not play music that is too stimulatory during your workout as there's no point in turning it into a HIT workout, or stressing your body through motor-music-emotional manipulation. It is important to mention that in time-restricted scenarios, two handed alternating or simultaneous dumbbell ULTRAS can be performed, although it would destroy my newly beloved acronym, many locomotive upper body aerobic exercises can be performed with two hands, such as dumbbell curls, or wrist curls, whereas walking bent-over rowing with dumbbells would be quite difficult.

[See: IMC Workout Protocols: NEURAL]

Note: Originally this exercise method was called ASSAULT, and although people may think I was inspired by Assault bikes (those that utilize a push and pull lever mechanism), this is untrue, as I was instead inspired by the original innovator of lower body cardiovascular exercise combined with upper body resistance training, that being *SoulCycle*. I have therefore changed the name and acronym of this method to avoid confusion, and because I find Assault bikes too damaging (high resistance) for the upper body muscles I do not want to be associated with their product, similarly to traditional rowing machines. That is not to say Assault bikes are not excellent tools for HIT cardio, but that my protocol is based on and around *Aerobics*, and because of this they serve an opposite role in principle and in action.

Micro-Essays

Ancient Medicine

The Chinese Meridian System (A component of Traditional Chinese Medicine: TCM) describes a flow of energy through the body, affecting both mind and body. Many skeptics have rightly and wrongly relegated this ancient medicine to the pseudoscience branch of science. But I have discovered a potential clue to the validity of its medical merits; It is possible that these "Meridian" points on the body are in fact locations near Lymph nodes, or near Lymphatic Vessels.

The Lymphatic System is described as "The tissues and organs that produce, store, and carry white blood cells that fight infections and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells)." This system is responsible for fighting infections through the activation of the immune system (macrophages/cytokines), with its most important purpose being the destruction of cancer cells.

The therapeutic efficacy of Cupping Therapy, which is considered by many to be quackery, has now been validated and shown to promote lymph vessel growth. This development must then bring Acupuncture into a new light and make us heed the wisdom of ancient medicine. For Hippocrates suggested in the 5th Century that weather effects health, an observation on his part that happened over 1500 years ago, and it was only in the year 1646 that barometric pressure was discovered, and eventually atmospheric pressure, which has been scientifically correlated to changes in blood pressure and neuropathic pain.

Exercise: The Kinesiological Prometheus

Exercise is directly related to locomotion, and for millions of years locomotion has been necessary for our species survival, to forage, to hunt, to wage war. Exercise is therefore imprinted into our DNA, making it an absolutely essential part of human existence to delay cellular aging and most importantly to promote cognition.

The evolutionary result and the current primary purpose of exercise is to enhance neurological adaptation through increased neurogenesis and synaptic function. This was only made possible through the *attrition of predation* our greatest ancestors experienced. I call this phenomenon the **Neuro-Cardio-Adaptation Hypothesis**.

This hypothesis explains the archetype masculine instinct to engage in competitive, high stress, and often violent sports and other forms of exercise, which are the recapitulations of the phylogenetic memories of the amygdala fight response, whereas the archetype feminine instinct during exercise is the polar opposite of the masculine, in that they prefer low stress (low cardiovascular threshold) uncompetitive sports, and most importantly,

group fitness classes, due to genetically encoded memories of the "Tend-and-Befriend" response (a novel threat response posited by Dr. Shelley Taylor), which describes the heightened caretaking that mothers engage in regarding their offspring when under threatening stimuli. Of course, variations exist in behavioral predispositions, but this is explained by psychological conditioning and not genetics.

My hypothesis also explains the discrepancies in *average* neuron populations between men and women, as women tend to have around 1.5 billion less neurons than men, because throughout time their female ancestors have primarily activated and utilized the flight / Tend-and-Befriend threat response during times of extreme stress and physical confrontation, leading to far less cardiovascular-intensive exercise occurring, and resultant exercise-induced increases in neurogenesis. To clarify a question that is sure to arise from the aforementioned observation; Psychological stress may raise heart rate, but it does so pathologically, whereas exercise stimulates heart rate while simultaneously stimulating the release of myokines, and many other growth factors that promote cellular adaptation.

Heart attacks are the leading cause of death in women, likely due to the increased activity of the emotional intelligence centers in females, but also in my opinion because of the lack of the fight response, as behavioral passivity is an unrecognized cellular poison.

The highest intensity forms of cardio stimulate the greatest increases in neurogenesis, whereas the lower intensity forms of cardio stimulate neuroprotection and memory processes. This means that for our ancestors, humanoid or not, the most high intensity, traumatizing, and violent experiences of engaging in physical confrontation, the act of hunting on foot during the early Paleolithic period, or the act of fleeing from predators during the Mesozoic Era, elicited the greatest increases in brain cell growth, which promoted long term memory formation, and is likely to have contributed to the increased density of neurons in our brains over time, whereas lower intensity forms of cardio such as the manual labor that accompanied foraging or migration patterns facilitated primarily memory acquisition, with both forms of cardio-based neurological adaptation being essential for survivalism.

In conclusion, I believe that the high intensity cardiovascular exercise that our earliest ancestors engaged in, similarly to mitogenic effects ROS, when intermittently experienced, clearly promoted amazing adaptation and stress resilience through physical brain expansion and increases in brain connectivity.

[See: Specialization, Cardio, Injuries, & Antagonist Muscle Activation]

[A] Cardiovascular Exercise is more effective at promoting cognition than neurotrophic chemicals.

"<>Nutrition and physical exercise can enhance cognitive function but the specific combinations of dietary bioactives that maximize pro-cognitive effects are not known nor

are the contributing neurobiological mechanisms. Epigallocatechin-3-gallate (EGCG) is a flavonoid constituent of many plants with high levels found in green tea. EGCG has anti-inflammatory and anti-oxidant properties and is known to cross the blood brain barrier where it can affect brain chemistry and physiology. β-Alanine (B-ALA) is a naturally occurring β-amino acid that could increase cognitive functioning by increasing levels of exercise via increased capacity of skeletal muscle, by crossing the blood brain barrier and acting as a neurotransmitter, or by free radical scavenging in muscle and brain after conversion into carnosine.
<>The objective of this study was to determine the effects of EGCG (~250mg/kg/day), B-ALA (~550mg/kg/day), and their combination with voluntary wheel running exercise on the following outcome measures: body composition, time to fatigue, production of new cells in the granule layer of the dentate gyrus of the hippocampus as a marker for neuronal plasticity, and behavioral performance on the contextual and cued fear conditioning tasks, as measures of associative learning and memory. Young adult male BALB/cJ mice approximately 2months old were randomized into 8 groups varying the nutritional supplement in their diet and access to running wheels over a 39day study period.
<>Running increased food intake, decreased fat mass, increased time to exhaustive fatigue, increased numbers of new cells in the granule layer of the hippocampus, and enhanced retrieval of both contextual and cued fear memories. The diets had no effect on their own or in combination with exercise on any of the fitness, plasticity, and behavioral outcome measures other than B-ALA decreased percent body fat whereas EGCG increased lean body mass slightly.
<>Results suggest that, in young adult BALB/cJ mice, a 39day treatment of exercise but not dietary supplementation with B-ALA or EGCG enhances measures of fitness, neuroplasticity and cognition."[539.B1]

[B] Acutely administered SSRI are nearly always beneficial towards cognition, as discussed before, because the Serotonin receptors are not desensitized, but we see in this study that chronic running exercise is able to rapidly reverse the neurotoxic effects of chronic unpredictable stress by promoting myelination.

"<>Although selective serotonin reuptake inhibitor (SSRI) systems have been meaningfully linked to the clinical phenomena of mood disorders, 15-35% of patients do not respond to multiple SSRI interventions or even experience an exacerbation of their condition. As we previously showed, both running exercise and fluoxetine reversed depression-like behavior. However, whether exercise reverses depression-like behavior more quickly than fluoxetine treatment and whether this rapid effect is achieved via the promotion of oligodendrocyte differentiation and/or myelination in the hippocampus was previously unknown.

<>Sixty male C57BL/6 J mice were used in the present study. We subjected mice with unpredictable chronic stress (UCS) to a 4-week running exercise trial (UCS + RN) or intraperitoneally injected them with fluoxetine (UCS + FLX) to address these uncertainties. At the behavioral level, mice in the UCS + RN group consumed significantly more sugar water in the sucrose preference test (SPT) at the end of the 7th week than those in the UCS group, while those in the UCS + FLX group consumed significantly more sugar water than mice in the UCS group at the end of the 8th week. <>The unbiased stereological results and immunofluorescence analyses revealed that running exercise, and not fluoxetine treatment, increased the numbers of CC1+ and CC1+/Olig2+/BrdU+ oligodendrocytes in the CA1 subfield in depressed mice exposed to UCS. Moreover, running exercise rather than fluoxetine increased the level of myelin basic protein (MBP) and the G-ratio of myelinated nerve fibers in the CA1 subfield in the UCS mouse model. Unlike fluoxetine, exercise promoted hippocampal myelination and oligodendrocyte differentiation and thus has potential as a therapeutic strategy to reduce depression-like behaviors induced by UCS."[539.B2]

Rest Periods & Failure Training: Do They Matter?

[A] It's quite clear to the average powerlifter that longer rest periods are beneficial to muscle growth, or at the very least, CNS recovery between sets, and this idea turns out to bear merit, as longer rest periods result in potentiated myogenesis. This is likely explained by magnified post-exercise mTOR expression versus AMPK. Although it is up for debate whether longer rest periods would benefit an individual engaging in Lactic acid Training, where the volume is high.

[B] Training to failure each set with higher loads is a bad idea, because when the CNS is fatigued recovery between exercise sessions is delayed. As to what effect high load failure training / short rest period high load training will have on the neuromuscular synapses, I do not know. Regardless, the goal of resistance training for most is to grow muscles, not to condition them, and therefore it is my opinion that for conditioning a muscle group, one must first decide on what type of conditioning is sought after: Is it neuromuscular junction growth? If so, then one will use low load, high volume explosives with resistance bands, imitating the act of "sprinting". Or is it strength-endurance, which is the number of repetitions you can perform in one set; If so, you would perform moderate load, high volume Superslow Concentricity Training to complete failure to grow your slow twitch fibers, or engage in high volume LAT to exhaust and adapt your glycogen stores.

Now the question presents itself; If longer rest periods between high load training (singles) is a proven method to increase absolute power, how long is too long? Why not

take fifteen-minute rest periods between sets, or twenty, or thirty? It does not make sense to suggest that when the blood leaves a muscle, the chance for injury substantially increases, because injuries are far more dependent on prior exercise-induced muscle damage, exercise form, and time-under-tension, but what if the loads lifted are within reason, such as 50% of your 1RM? Will a rest period as long as sixty minutes enhance myogenesis? Olympic Lifters often take very long rest periods between performing singles, although this only indicates that the CNS adapts more readily to intermittent and high intensity exercises, but longer rest periods do not only allow the CNS to better adapt to training, they also mitigate neuronal fatigue, meaning that more conscious effort can be applied towards the motor control of an exercise after each successive set or repetition, leading to better exercise form, which is likely the *primary* reason why longer rest periods promote strength and power gains over shorter rest periods, because to lift a high load weight efficiently requires precise control of biomechanics, which requires a strong mind-muscle connection, which is often dependent on neurological fatigue levels.

[A] "<>The purpose of this study was to investigate the effects of short rest intervals normally associated with hypertrophy-type training versus long rest intervals traditionally used in strength-type training on muscular adaptations in a cohort of young, experienced lifters. Twenty-one young resistance-trained men were randomly assigned to either a group that performed a resistance training (RT) program with 1-minute rest intervals (SHORT) or a group that employed 3-minute rest intervals (LONG). All other RT variables were held constant. The study period lasted 8 weeks with subjects performing 3 total body workouts a week comprised 3 sets of 8-12 repetition maximum (RM) of 7 different exercises per session. Testing was performed prestudy and poststudy for muscle strength (1RM bench press and back squat), muscle endurance (50% 1RM bench press to failure), and muscle thickness of the elbow flexors, triceps brachii, and quadriceps femoris by ultrasound imaging. <>Maximal strength was significantly greater for both 1RM squat and bench press for LONG compared to SHORT. Muscle thickness was significantly greater for LONG compared to SHORT in the anterior thigh, and a trend for greater increases was noted in the triceps brachii ($p = 0.06$) as well. Both groups saw significant increases in local upper body muscle endurance with no significant differences noted between groups. This study provides evidence that longer rest periods promote greater increases in muscle strength and hypertrophy in young resistance-trained men."[539.C]

[B] "<>Purpose: To describe the acute and delayed time course of recovery following resistance training (RT) protocols differing in the number of repetitions (R) performed in each set (S) out of the maximum possible number (P).
Methods: Ten resistance-trained men undertook three RT protocols [S × R(P)]: (1) 3 × 5(10), (2) 6 × 5(10), and (3) 3 × 10(10) in the bench press (BP) and full squat (SQ) exercises. Selected mechanical and biochemical variables were assessed at seven time

points (from - 12 h to + 72 h post-exercise). Countermovement jump height (CMJ) and movement velocity against the load that elicited a 1 m s^{-1} mean propulsive velocity (V1) and 75% 1RM in the BP and SQ were used as mechanical indicators of neuromuscular performance.
<>Results: Training to muscle failure in each set [3 × 10(10)], even when compared to completing the same total exercise volume [6 × 5(10)], resulted in a significantly higher acute decline of CMJ and velocity against the V1 and 75% 1RM loads in both BP and SQ. In contrast, recovery from the 3 × 5(10) and 6 × 5(10) protocols was significantly faster between 24 and 48 h post-exercise compared to 3 × 10(10). Markers of acute (ammonia, growth hormone) and delayed (creatine kinase) fatigue showed a markedly different course of recovery between protocols, suggesting that training to failure slows down recovery up to 24-48 h post-exercise.
<>Conclusions: RT leading to failure considerably increases the time needed for the recovery of neuromuscular function and metabolic and hormonal homeostasis. Avoiding failure would allow athletes to be in a better neuromuscular condition to undertake a new training session or competition in a shorter period of time."[539.D]

The Junk Food Paradox

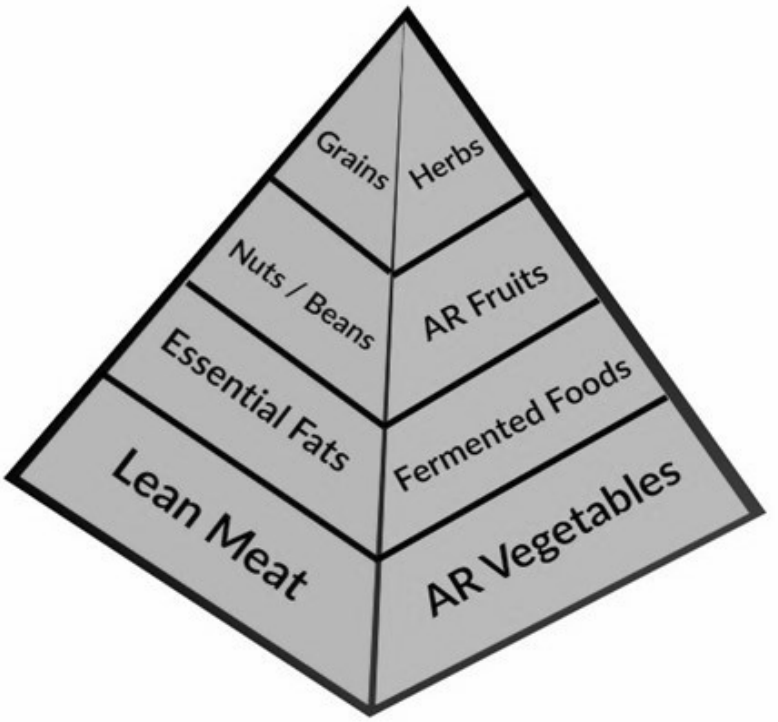
The most used excuse for bad diets in first world countries is the "too expensive to eat clean" one, where people will attest that buying organic, or healthy whole foods is just not economically feasible considering the perceived differences in price, and although it is true that the price of food has risen substantially over the years, "Shrinkflation" is real and noticeable for just about every brand of processed food, from cereal, to chips, to cookies, and even drinks, whereas whole foods have not shrunk in size, at least not to a noticeable extent, it is therefore unintelligent to continue to support food manufacturers not only because they reduce the quantity of food you receive without informing consumers, but also because these hyper processed foods cost so little to manufacture. Is it better to feed yourself, or your family, a meal composed of inexpensive white bread, fatty meat, & soy mayonnaise, over a smaller portion of multi-seed bread, a lean variety of meat, and an alternative mayonnaise? If you have a child (not infant), a higher carbohydrate diet is actually good for their neurological development, as covered previously, but if you are older, or your family is older, it does not make sense to sacrifice the purity of natural foods for *superficially inexpensive* processed foods. Is the price difference worth the reduction in health that accompanies bad dietary choices? I suppose it depends on the budget, if you're living in absolute poverty, processed foods may be the only choice to satiate hungry stomachs. Processed foods often are preferentially chosen over protein or phytochemical-rich foods because the taste of a food is more important to individuals and families than the nutrition or beneficial effects of foods, and this illogical neurological-dietary habit clearly comes from the snack foods

and oversweet drinks we are given as children, which psychologically condition us to seek out flavor first and foremost. Meals should be defined and formulated sequentially, firstly by health benefits, secondly by a balanced macronutrient profile, and thirdly by taste.

Why would you overpay for food that is made of ingredients that cost so little to acquire, such as flour or high fructose corn syrup? Ask yourself, is your addiction to name-brand ice cream, chips, or cookies unhealthy, or more importantly, is it not fiscally irresponsible? Could you not make the same foods at home for a fraction of the cost in stores, and could you not add ingredients that transform these junk foods into healthfoods, such as by including protein powders, GlySer, whole grains, essential fats, or herbal extracts in the recipes?

Displayed below is my ideal Food Pyramid, one that is sure to make you healthy.

(AR = Antioxidant Rich = Cruciferous Vegetables, Blueberries / Chokeberries, etc.)



YouTube Charlatans

Many pseudointellectual doctors and fitness personalities on YouTube feign an understanding of a certain phytochemical, drug, therapeutic technology, or other process, and they will go on to make videos, paraphrasing the positive or negative

pharmacodynamics or physiological effects of the aforementioned factors, and yet they will give no verbal reference to the scientist's actual words whose research they are supposedly reporting on. Instead, if they are gracious, they will include a small link in their videos, at the very bottom of the video descriptions, after copious amounts of textual advertising. These individuals wish to profit from breakthrough applied research, and in reality they do not care about the health of their listeners. They also show severe disrespect to the researchers whose work they profit off of, by attempting, often successfully, to associate a bevy of pharmacodynamic research to their name, their charismatic personality.

I take no issue with the necessity of public and advertised elaboration on interesting and relevant research articles, as for the uninitiated, it is often of supreme necessity for the spreading of knowledge. But I do take issue with individuals who attempt to steal the attention and praise from researchers, who spend months, and sometimes even years developing and acquiring the skills, knowledge, and funding that goes into creating a logically sound research article. YouTube Charlatans are those who do not attempt in any way to encourage intellectual self-sufficiency in their audience, they only wish to profit from their audience.

I implore the readers of this book to go on their own PubMed Journeys, unaccompanied by anyone else, as you will never become enlightened on how the brain and body work, or how chemicals effect the body, by subscribing to or listening to one man or woman who wish to be the subsidiary vanguards of science. One must dive into the deepest and darkest parts of the ocean (research databases) to find meaning in the chaos. It is wise to stay away from individuals who attempt to explain the intricacies of a study with *little or no reference to the source material*.

When I summarize a study, it is interconnected to the true complexity of the study (the scientists' actual words), it is never disconnected from it. I would never attempt to profit from clickbait junk such as "NAME REDACTED explains the hidden benefits of (insert herb, or chemical)" that so many individuals propagate on the internet, in which they or their podcast / talk show guests describe a science that they have no understanding of in hopes of gaining attention, fame, and profits, without providing one research article reference, for I am a compiler of knowledge, second to conceptualizer, and I live by the Socrates quote:

"*I neither know nor think I know what the gods know. But I do know that I don't know, and that's the extent of my knowledge.*"

In the end, you too will find out there is no panacea supplement or perfect therapy, and likened to the complexity of our brains, to achieve greatness requires innumerable numbers of positive contributing factors. No propriety blend of weak herbal extracts advertised by a well-dressed and well-spoken Charlatan is going to improve your life, except through the Placebo effect. Always seek out transparency and potency of supplement ingredients, and more importantly, do not support men and women who do not adequately reference the research of which they so confidently elaborate on, for they

are intellectual thieves. Remember, you do not need a "medical degree" to comprehend research articles—to engage in interdisciplinary analysis.

Exercise Chemical Conditioning

It is a severe mistake that many individuals consume or use chronic concentrations of caffeine, nicotine, THC, and alcohol when not being productive, when procrastinating. Recreational Drugs are best combined with intellectual work or exercise, for the obvious reason that if you aren't earning money from engaging in mentally exhausting work, or you aren't growing stronger, faster, leaner, or more enduring through exercise, and you're *high*, what are you doing with your life? This is why I suggest that all those who read this save their caffeine, nicotine, THC, and even alcohol use for intra-workout. By doing this you will be conditioning your brain to associate exercise with the greater release of pleasure chemicals, dopamine, and serotonin, thus programming your brain to seek out exercise to a greater degree. This will make you literally *work* for your drugs, which is something many people do not do, in terms of having unlimited access to a certain addictive chemical, which by all means is very unhealthy. The primary issue with utilizing Exercise Chemical Conditioning is that it may give you a false sense of confidence, of errored memory, that will push you towards overtraining, and eventual injury, which is why you should be aware of what you are doing in the gym, be conscious of what loads you are lifting and how much volume you are engaging in.

Is Absolute Strength Maintainable?

The science of absolute strength (muscle power: 1RM) is very difficult to understand, with most of us attributing the phenomenon to fast twitch fibers, which is only partly true, as absolute strength in modern man is explained by way of a combination of factors, such as fast twitch fibers, neuromuscular junctions, motor coordination (technique), CNS activity, and ergogenics, to name a few. No powerlifter or Olympic athlete has ever continued to increase their 1RM throughout their lifespan, inevitably they get injured, or their absolute strength begins to regress, and they are forced to deload, detrain, or retire.

Powerlifting successfully clearly requires above all else a high functioning Central Nervous System, but the CNS can be strengthened in a safer way aside from high frequency powerlifting, that being through HIT Cardio. Whereas the myoneural junctions can be strengthened safely through low load, high volume explosive resistance training with resistance bands.

In closing, I believe that it is ideal for any lifter focused on absolute strength growth or maintenance to restrict their lifting percentages to around 50% their 1RM for 90% or more of all workout sessions, to mitigate the risk of injury or overtraining.

Fructose & Palmitic Acid: The Compatriots of Survivalism

An enquiring mind may wonder to themselves why we have consumed fruit for millions of years, and our greater ancestors for billions of years, and why so many foods contain such high concentrations of Palmitic acid, such as vegetable oils, and meats. The truth is that both fructose and Palmitic acid serve the primary role of promoting adipogenesis, they are not random food toxins present in our environment. They served the role of promoting our survival and continue to serve that role in many impoverished nations, because a 21st century individual living in a first world nation, with an adequate food supply, will never understand the absolute necessity of adipose tissue.

It is adipose tissue that provides us the energy substrate to survive during times of starvation, and had we not had access to fruit or high saturated fat meats, nuts, and dairy products, many of our ancestors would not have survived their journey through the harsher realities of the past, and you yourself would not exist today, as the body and brain must have energy to function, and adipose tissue is the greatest source of energy in times of scarcity.

Even though these chemicals promote many forms of aging when consumed in excess, they are not to be considered enemies of nutrition, but they are unnecessary fuel sources for individuals who have enough wealth, and resultant freedom, to choose what they eat.

Warmups, Injury Prevention, Exercise Flexibility

Performing a large amount of high volume-low load warmups before every workout will not prevent injury if you train with an improper technique during your working sets or if you consistently overtrain, but high frequency weekly IMC Warmup sessions will magnify post-exercise myogenesis and potentially accelerate muscle regeneration, but that’s not because of the blood that flows into the muscle intra-warmups, it is a result of the blood vessels that form post-workout. One must remember that aerobic exercise is angiogenic, which is why it should never be neglected.

Preventing injuries efficiently will always be dependent on behavioral flexibility. The ability to change how you exercise or how often you train is a sign mental strength. Most musculoskeletal injuries present themselves acutely, and subtly, with a dull ache or slight pain, and most athletes ignore these warning signs not because of sheer willpower or drive, but dangerous comfortability, the comfort in maintaining a certain exercise program, of maintaining a habit, a *behavior*. Enhanced exercise flexibility is the hallmark sign of the most successful athletes who show physical fitness longevity, for they possess the intelligence to scale back exercise intensity, exercise volume, or completely change their exercise types during periods of injury.

ULTRAS: Hike & Curl

My favorite health promoting exercise to engage in with my family, and to engage in when I am too tired or stressed to follow one my workout protocols, is what I call "Hike & Curl". Forest Bathing as you now know is a wonderful way to rejuvenate the mind and body, and scheduling hikes into your workout protocols is a wonderful idea to regain your connection to nature, but I have always found my hikes to be missing something. As it turns out, the hamstrings share a similarity to the biceps, in that we train them at a high frequency, whether in the gym, at home, or at work, but the biceps unfortunately do not experience the same amount of aerobic volume as the hamstrings do, making them far more prone to injury, and worse, overtraining-induced atrophy. Thus, I began to carry one 1LB dumbbell with me on my hikes, performing strict unilateral curls, alternating curl exercises, alternating ROM, and of course changing arms after each set (50-300 Repetitions) as I walked.

I will tell you that my biceps have grown through performing these aerobics a few times a week, and they feel far healthier. Consider trying it out, especially if you are too tired or depressed to follow a workout protocol on certain days, or if you are generally uninterested in most forms of exercise.

As a note, please be intelligent and do not use a dumbbell over 2LB's as you will assuredly overtrain, especially if your hikes last longer than thirty minutes.

See: ARCS, Cardio, Injuries, & Antagonist Muscle Activation: ULTRAS.

Color: The Intensity of our Thoughts

Colors are ubiquitous on earth, they often define our age, our sex, and our personality. The electromagnetic waves (light) that make up "colors" actually do not possess colors, but they are identifiable to our brains by their wavelength, for example the wavelength associated with the color red is 620-750 nanometers, whereas the wavelength associated with the color blue is 450-520 nanometers. Objects possess colors because of their varied molecular composition, electron transitions, electron absorption, and end resulting reflected wavelengths, meaning even a toy figurine is bristling with energy. The concurrent reflected electromagnetic waves of environmental matter enters our eyes through the photoreceptors and are processed in our occipital lobe, and differentiated by wavelength, thus creating the strange and beautiful perceptions of the color spectrum.

Through millions of years of retroviral infection and actual morphogenic evolution (not Darwinian Natural Selection) beginning during our earliest mammalian evolutionary stage, when our ancestors were shrew-like creatures living in the age of reptiles, the Mesozoic Period, they possessed Monochromatic vision, that is to see only black and white, and then came the development of Dichromatic vision, to see blues and yellows,

and then the Australopithecus hominins developed Trichromatic vision, to see reds (the full spectrum of colors).

Around 12% of human women tend to have a fourth photoreceptor, whereas men tend to have only three, giving these women a greater ability to distinguish and differentiate colors in their environment. This gender specific evolutionary advantage towards color comprehension is currently posited to be a result of Foraging for food (locating ripe fruits), and reproductive visual acuity (to analyze a potential mates physical health). It is not a coincidence that most women possess greater color comprehension and also statistically tend to be more "open minded" in their religious and political outlooks, whereas men tend possess more focused and polarized religious and political outlooks (leaving hormones aside). Does this mean that color is associated with divergent thinking? Possibly, but moreso it is provably associated with the intensities of thoughts—the intensity of emotions, such that the archetype boy chooses to adorn himself in blue clothing, and the archetype girl choses pink or purple clothing. It is not necessarily certain colors that associate with conditioned or epigenetically programmed gender expressions, but instead certain wavelengths, which associate with certain patterns of neural oscillations (behaviors, thoughts).

Through enhanced color comprehension females have reached a new level of visual evolution that is often unrecognized, an evolution in the divergence and differentiation of thinking. This visual evolution was surely beneficial to the most ancient of female ancestors, but in our current century, we must wonder if an improved ability to discriminate between colors is an aid or a detriment for a modern woman. Whereas an ancient female hominin would use her keen eyesight to forage for edible fruit and vegetables, the 21st Century woman forages in the Home Depot by comparing all the various shades of teal in a paint color deck for use in her interior design project. Is the opulence and overabundance that comes from technologically and economically evolved societies to be considered antithetical to physical evolution?

Color is used by megacorporation's to subliminally manipulate their consumers, to play with their emotions, to strengthen or weaken certain thought patterns, such as those related to hunger, thirst, fear, or comfort. Even something as seemingly inconsequential as common brick-and-mortar interior store lightening drastically affects our mood and memory, such that lower end and less liked stores tend to have more neutral fluorescent lighting leading to more blue light emittance and greater color discrimination, the higher end or more well liked varieties of stores tend to use warm fluorescent lighting leading to more yellow light emittance and reduced color discrimination equating to less resultant mental stimulation i.e. a more comfortable and casual shopping experience. People tend to associate the clientele of a store with the atmosphere of a store, but the lighting of a store is a far more potent influence on the illusionary subjective pleasantness of the human shopping experience.

Our color choice in our daily dress is not only an expression of our personality, but an actual affecter of our moods and emotions throughout the day, selfsame to those we

encounter as we can alter the affections of those around us to excite, or sooth their minds, however subtly the changes may be.

The Diets of Children

The nutrition of an infant will surely effect the intelligence that they display in later life, in that an infant raised on a diet of processed foods and sugars and devoid of essential nutrients will undoubtedly suffer from what I consider to be a *missed neurogenic opportunity*—The opportunity to enhance neurogenesis, synaptogenesis, neuritogenesis, myelination, and brain connectivity. The opportunity that comes to fruition in later life to allow their developed minds to analyze the world and deduce from its infinite complexity a logical path to tread. To feed your baby foods rich in vitamins, minerals, probiotics, and more importantly, foods rich in neurotrophic antioxidants, such as wild blueberries, will help them to survive and thrive in later life.

For those who were raised with inferior diets, death comes quickly, not merely in the form of organic disease, such as heart disease, or neurodegeneration, but instead intellectual deficiency. For a brain that does not function properly will often make incorrect socio-economic and interpersonal decisions, leading to unnecessary psychological stress and suffering. Suffering is not always a bad thing, but for many individuals it is a progressive poison rather than a life lesson, and for that reason we should strive to enhance the intelligence of our children through any and all means available. To chemically alter and bless their brains with a greater ability to learn, to overcome life's psychological obstacles more efficiently.

Why do many parents with children who suffer from aberrant mental conditions often feed them terrible diets of processed foods and drinks and exclaim when asked why their children do not eat vegetables and fruit that "they won't eat anything else!"?
Children do not crave what they have never eaten, nor do they frequently crave food items they have rarely eaten. It is the job of parents to feed their children copious amounts of lean meats, antioxidant rich fruits, & vegetables, whether fresh, cooked, or fermented, to strengthen their immune systems, and their brains. Even if a child naturally despises the taste of broccoli, try cauliflower, if that fails try cabbage, and so on and so forth until you come to vegetables they prefer.

A parent who shows obvious disgust towards healthy foods while eating them, when in the company of a developing child, is damaging that child's future health resilience, and should be ashamed of themselves. A child is not capable of controlling what he or she eats, they either take after their parents who often themselves eschew phytochemical rich foods, or they learn to manipulate their parents into continuing to buy ultraprocessed food, thereby unintentionally exacerbating their intestinal florae dysbiosis (unhealthy intestinal microbiome) and neurological deterioration. Psychological conditioning is a

power all parents must comprehend if they wish to raise children with optimal health resiliency.

The Biomedical Baby

It is possible through a cursory understanding of ergogenic and phytochemical pharmacodynamics to enhance your infants intelligence through careful supplementation during their earliest stages of growth in utero.

Note: If your child's neurological development is impaired or delayed in any way, it is a clear sign that you need to increase their dietary intake of vitamins, minerals, and most especially essential fatty acids, such as ALA, LA, DHA, and EPA.

Please do not use alcohol, caffeine, THC, or nicotine while pregnant.

1. Pregnancy Cycle Diet & Supplementation: Essential Nutrients, copious amounts of dietary Alpha Linolenic acid (20 Grams or more per day) (Chia seed Pudding, Chia seed oil Smoothies, Flaxseed Breads, Flax Milk, Etc.), Fish oil high in DHA/EPA, and a Linoleic acid-rich oil added to each meal. No Soy Protein, Limited consumption of Palmitic acid-rich food and Fructose. Lactobacillus fermented foods and Lactobacillus probiotics may be consumed and used safely, I believe, and if these beneficial Extracellular Vesicles produced by *good* intestinal florae pass through the placental barrier, they may promote neurogenesis in the baby.
Hydroxytyrosol may promote fetal brain neurogenesis, therefore consuming an EVOO high in this compound may be intelligent while pregnant:

"<>Supplementation of a mother's diet with antioxidants, such as hydroxytyrosol (HTX), has been proposed to ameliorate the adverse phenotypes of fetuses at risk of intrauterine growth restriction. In the present study, sows were treated daily with or without 1.5 mg of HTX per kilogram of feed from day 35 of pregnancy (at 30% of total gestational period), and individuals were sampled at three different ages: 100-day-old fetuses and 1-month- and 6-month-old piglets. After euthanasia, the brain was removed and the hippocampus, amygdala, and prefrontal cortex were dissected. The profile of the catecholaminergic and serotoninergic neurotransmitters (NTs) was characterized and an immunohistochemical study of the hippocampus was performed. <>The results indicated that maternal supplementation with HTX during pregnancy affected the NT profile in a brain-area-dependant mode and it modified the process of neuron differentiation in the hippocampal CA1 and GD areas, indicating that cell differentiation occurred more rapidly in the HTX group. These effects were specific to the fetal period, concomitantly with HTX maternal supplementation, since no major differences remained between the control and treated groups in 1-month- and 6-month-old pigs."[539.D0]

1.2 Pregnancy Cycle Exercise: 60-Minutes Steady-State Cardio @ 65% Max Heart Rate every day (after approval from the overseeing Doctor). It is my hypothesis that if a pregnant woman engages in safe (likely stationary) lactic acid accumulating exercise, such as using a recumbent bike, that the lactic acid in her blood will reach her babies brain by bypassing the placental barrier and promote neurogenesis. Aside from this hypothesis, a pregnant woman who engages in extended steady-state cardio will surely promote placental function, thereby enhancing nutrient delivery to her babies brain, and research bears some merit to these ideas:

"<>Background: Maternal physical activity during pregnancy could alter offspring's IQ and neurodevelopment in childhood.
<>Methods: Children belonging to a birth cohort were followed at 3, 12, 24 and 48 months of age. Physical activity during pregnancy was assessed retrospectively at birth. Neurodevelopment was evaluated by Battelle's Development Inventory (12, 24 and 48 months) and IQ by the Weschler's Intelligence Scale (48 months). Neurodevelopment was based on Battelles' (90th percentile) and also analyzed as a continuous outcome. IQ was analyzed as a continuous outcome. Potential confounders were: family income, mother's age, schooling, skin color, number of previous births and smoking; and newborns': preterm birth, sex and low birth weight.
<>Results: From birth to 48 months, sample size decreased from 4231 to 3792. Crude analysis showed that IQ at 48 months was slightly higher (5 points) among children from active women. The Battelle's score at 12 and 24 months was higher among offspring from active mothers. After controlling for confounders, physical activity during pregnancy was positively associated to the Battelle's Inventory at 12 months IQ, however, at 48 months no association was observed."[539.D0.1]

2. Infanthood-Early Childhood Cycle: Safe food antioxidants such as fruit polyphenols, also probiotics, and prebiotics; Wild Blueberries, Homemade Sweet Potatoes, Alpha-Linolenic acid: Chia Seed / Flax Seed oil added to sweetened foods or smoothies (Banana-Blueberry Shakes, Pastries, Breads, Etc.), Yogurt, Kefir, Skim Milk (Any other source of Lactose), Cottage Cheese, Oatmeal, Rye / Oat Bread. Supplements should be centered around Essential Nutrients (most especially Ascorbic Acid, D3, Vitamin K1/K2, Potassium, Vitamin B1-2-3-5-6-7-9-12, ALA enriched foods, LA plant oils, a lot of amino acids), and finally Lactobacilli Probiotics only.
Remember earlier in this book you learned that newborns do not possess adequate pancreatic development to secrete insulin, therefore it is a very bad idea to give your baby large amounts of unhealthy fruit juices (except for wild blueberry juice), or other fast digesting carbohydrates, I would suggest sticking to skim milk and whole foods that have been pureed such as Sweet Potato baby food. I believe that insidious hyperglycemia in infanthood is a contributing factor for decreased Intelligence Quotients in later life, likely because of the decrease in brain blood vessel density that is surely to occur in these unfortunate babies, but only time will tell if my hypothesis is correct.

L-Theanine may promote neurogenesis in developing brains, and if administered chronically (consumed slowly all day), is likely to enhance the intelligence of your baby. I would suggest a dosage of 20-40mg per day, never acutely administered to avoid withdrawal-induced mood changes, but instead added to a large reservoir of water or milk that the child can drink from throughout the day and night:

"<>Theanine, γ-glutamylethylamide, is one of the major amino acid components in green tea. In this study, cognitive function and the related mechanism were examined in theanine-administered young rats. Newborn rats were fed theanine through dams, which were fed water containing 0.3% theanine, and then fed water containing 0.3% theanine after weaning. Theanine level in the brain was under the detectable limit 6 weeks after the start of theanine administration. Theanine administration did not influence locomotor activity in the open-field test. However, rearing behavior was significantly increased in theanine-administered rats, suggesting that exploratory activity is increased by theanine intake.
<>Furthermore, object recognition memory was enhanced in theanine-administered rats. The increase in exploratory activity in the open-field test seems to be associated with the enhanced object recognition memory after theanine administration. On the other hand, long-term potentiation (LTP) induction at the perforant path-granule cell synapse was not changed by theanine administration. To check hippocampal neurogenesis, BrdU was injected into rats 3 weeks after the start of theanine administration, and brain-derived neurotropic factor (BDNF) level was significantly increased at this time. Theanine intake significantly increased the number of BrdU-, Ki67-, and DCX-labeled cells in the granule cell layer 6 weeks after the start of theanine administration.
<>This study indicates that 0.3% theanine administration facilitates neurogenesis in the developing hippocampus followed by enhanced recognition memory. Theanine intake may be of benefit to the postnatal development of hippocampal function."[539.D0.2]

Biomedical Research: The Linear A of Tomorrow

The National Center for Biotechnology Information (NCBI) is controlled by the National Institutes of Health (NIH), a US Government agency and propaganda factory for the promotion of hypercomplex prophylactic viral vector or mRNA-based *medicines* that may cause autoimmunity, neurodegeneration, or death due to the stimulation of massive amounts of inflammatory cytokines, and interferons.
The NCBI hosts PubMed, the largest database of biomedical literature available currently, and because of the sheer complexity of the different sciences elaborated on in each individual article, censorship is often difficult, which is a good thing, because even though a small number of popular research articles are based upon conflated variables, or lead to misguided conclusions, or are full of outright lies, many more offer to us

revelations in knowledge that are unknown to both the educated and the non-educated. Contradictory research, the sort that goes against pharmaceutical products and Governmental goals will increasingly be suppressed and barred from publishing, for all scientific knowledge eventually becomes polarized by politics even if it is unbiased in its true nature, many human beings in positions of authority will seek to destroy novel information to avoid freedom of thought.

Biomedical Research is as of now, a relatively undeciphered language, while many large organizations claim supremacy over it, far more singular minds are beginning to comprehend it more effectively each day, often intuitively. To keep an open mind towards our social or sexual inclinations is taught to be virtuous, but to question the science that Governmental medical institutions spew is considered dangerous, or evil, which is an irony not lost to me.

Human creativity can be applied in many different ways, and in first world nations it is harnessed by most citizens in creating and consuming fictional works of art that mesmerize us into forgetting or ignoring the anxiogenic complexities of existence, the power plays of politicians, and the subliminal advertising of mega corporations. To question a scientific conclusion, if it has achieved a wide reaching consensus, is not illogical, or morally wrong, it is intelligent, as there exists within every scientific discovery nuances that are as of yet undiscovered—complexities that have not been elaborated on. To permit our Governments to continue acting as the vanguards of our biomedical knowledge is the subtlest path to tyranny.

I would never suggest Inflammation Cycling as simply being "Safe & Effective", for that would make me guilty of the *Argumentum ad passiones* (Appeal to emotion) logic fallacy, as Robert Malone clarified in a talk he gave at the Mises Institute, the words used in the advertising of experimental therapeutics are not chosen randomly but hold a deeper and darker meaning used to manipulate the masses into medical compliance.

Fasting, Detoxification, & "Fasting Diets"

For many years the naturopathic community and medical professionals in the alternative medicine sphere have promoted fasting to reduce inflammation, to "detoxify" the body, and extend lifespan, but previously we have learned that fasting requires and promotes inflammation to exert its most beneficial effects, those being lipolysis and angiogenesis, secondarily to autophagy. We must understand that fasting in all its incarnations is generally beneficial to unhealthy individuals because of the *restriction* of unhealthy food (and macronutrients in general) that accompanies a "fast", not because of substantial changes to the body brought on by enhanced cellular detoxification and rejuvenation, the former of which is actually fasting-induced autophagy, that of which if not combined with exercise is inefficient.

If a man or woman is unwilling to restrict their consumption of unhealthy food or drink, then fasting therapy is an ideal countermeasure to their dietary inflexibility. But if they are capable of controlling what they put in their mouths, then a diet composed of primarily cruciferous vegetables, and raw foods low in carbohydrates and high in phytochemicals will benefit their health far more than fasting will. In many scenarios because of poverty, a person is unable to control their diet, and they do not have the option to restrict the amount of high carb or high non-essential fat foods they eat. They can, however, easily engage in intermittent fasting to reduce the physiological burden of dietary excess, or engage in prolonged fasting to save money, to sacrifice themselves for the satiety of their loved ones. But even if health indices improve in fasted individuals who remain on bad diets, they are still on a downward spiral that will eventually and invariably end in the development of one or more diseases (unless their physical activity level is extremely high).

To clarify my point, short term fasting may exert subtle antioxidant effects, but this is primarily due to the restriction of macronutrients, which causes a transient decrease in ROS by way of reduced beta-oxidation electron leakage.

Many supposed fasting protocols and ketogenic diets paradoxically suggest consuming small amounts of fruits, fruit juices, or starchy soups during the diets, but this is ridiculously uninformed and illogical advice, for even a minute amount of fructose added to a diet will knock the body out of ketosis[2] and hamper beta-oxidation[3], meaning that consuming any fructose on a fast, or a ketogenic diet, will substantially suppress lipolysis and potentially magnify muscle catabolism.

Fasting should be treated as an emergency lipolytic therapy, a novel angiogenic therapy, or an advanced level longevity therapy, but not as a cellular *detoxifier* or replacement for a healthy diet. High volume exercise is in fact the true systemic *detoxification initiator* that stimulates both Autophagy and Mitohormesis.

[1] "<>The purpose of this study was to compare the metabolism and antiketogenic properties of fructose, glyceraldehyde, and sorbitol. Fructose, glyceraldehyde, and sorbitol were readily metabolized and exhibited an antiketogenic effect in both blood and liver when injected intramuscularly to starved (forty-eight hours) rats. Sorbitol had the most pronounced antiketogenic effect and produced an 80 to 90 per cent decrease in the blood ketone bodies sixty minutes after administration.
<>Fructose and glyceraldehyde were equally effective and produced about a 60 to 70 per cent decrease in ketone bodies. Fructose, glyceraldehyde, and sorbitol caused a significant decrease in the concentration of hepatic ketone bodies. In liver, sorbitol was found to be most effective in its antiketogenic action. The concentration of plasma free fatty acids remained unchanged after injection of all three antiketogenic substrates.

<>Fructose, glyceraldehyde, or sorbitol caused increased blood lactate and pyruvate concentrations, and fructose was the most effective of the three substrates. Fructose administration resulted in a significant decrease in hepatic lactate/pyruvate and beta-OH-butyrate/acetoacetate concentration ratios, whereas sorbitol caused an increase in the concentration ratio of these two substrat pairs. Decreases in blood and liver ketone body levels were associated with lowering of liver acetyl-CoA concentration . However, the decrease in hepatic acetyl-CoA produced upon the administration of antiketogenic substrates was not pronounced. Sorbitol administration resulted in the most pronounced increase in hepatic alpha-glycerophosphate concentration. Fructose or glyceraldehyde also caused an increase in alpha-glycerophosphate content. <>Administration of each of the three antiketogenic substrates produced an increase in hepatic dihydroxyacetone phosphate concentration. All three antiketogenic compounds increased liver glycogen and blood glucose concentrations. No significant changes were observed in hepatic ATP, ADP, or AMP concentrations sixty minutes after the injections of any of the antiketogenic substrates. Although decreased liver acetyl-CoA levels were associated with the antiketogenic effects of the compounds tested, the increased liver alpha-glycerophosphate content best explains the differences between fructose or glyceraldehyde and sorbitol."[539.D1]

[2] "<>The effects of fructose on the oxidation of [1-(14)C]palmitate in a rat liver mitochondria-high speed supernatant system have been investigated. This model system permitted study of the direct effects of fructose and the metabolism of fructose on fatty acid oxidation in the near absence of fatty acid esterification. Fructose inhibited the utilization of albumin-bound [1-(14)C] palmitate in the mitochondria-supernatant system, but did not affect fatty acid utilization by isolated liver mitochondria.
<>Although fructose decreased the ATP content in the mitochondrial-supernatant system, the level of ATP throughout the incubation period was sufficient for maximal fatty acid activation. Fructose decreased the conversion of [1-(14)C]palmitate to 14CO2 and depressed the formation of total labeled oxidation products (14CO2 + 14C-labeled ketone bodies) in this system. The results suggest that fructose metabolism inhibited fatty acid oxidation in the mitochondria-supernatant system by competitive substrate oxidation and thereby decreased utilization of the added [1-(14)C]palmitate.
<>The inhibition of L-[L-(14)C]palmitoylcarnitine oxidation, fructose was in all respects similar to its inhibition of palmitate oxidation, indicating that the site of fructose interaction was within the beta-oxidation sequence. These observations support the concept (Ontko, J.A. [1972] J. Biol. Chem. 247, 1788-1800) that the reciprocal changes in esterification and oxidation of palmitate caused by fructose in liver cells are primarily mediated via inhibitory effects on long-chain fatty acid oxidation."[539.D1.1]

Cardio, AMPK, & Catabolism

It has been taught that "too much cardio burns muscle"—that extended duration cardiovascular exercise is catabolic towards muscle tissue, and that a bodybuilder or powerlifter should limit their cardio to at or under thirty minutes per day. This old idea does have some scientific basis in reality, considering cardiovascular exercise increases AMPK expression, and AMPK reduces mTOR expression, and this systemic change would negatively impact myogenesis. But AMPK is not simply a catabolic agent, it does promote certain forms of myogenesis, and AMPK expression can be controlled quite easily through diet or supplementation. Even if we are to consider AMPK as purely catabolic, it is not difficult to increase mTOR expression through the consumption of copious amounts of amino acids, especially GlySer, each day, and this fact therefore overcomes the previous argument against cardio.

I believe that people are confused about what I call the *Local Cardio Effect*, versus the *Systemic Cardio Effect*. The Local Cardio Effect explains the changes to muscle fiber type a specific group of muscles experience during cardio training, such as the leg muscles being trained through the stair stepper. If a man gains substantial satisfaction from squatting super high loads, he may very well sabotage his myogenic or neuromuscular-synaptic growth by engaging in hours of lower body cardio each week, in conjunction with his normal training, not merely because of overtraining, but because of muscle fiber changes (fast to slow transformations). The Systemic Cardio Effect describes the physiological immunological and neurological changes that accompany cardiovascular training. This effect explains the acceleration of wound healing that occurs following high frequency moderate intensity cardio. To avoid the negative consequences of the Local Cardio Effect on muscle power or strength, if the cardio exercise in question is performed at a high frequency, one should utilize ARCS. For all other scenarios, low to moderate intensity cardiovascular training is only beneficial to a muscle group, considering it is high volume micro-reps, it is angiogenic, and will only delay muscle aging.

It is my analytical opinion that if someone is focused solely on muscle growth, the addition of cardiovascular exercise to their workout protocol, especially in the 60-63% Max-HR range, performed at a steady-state, will contrary to antiquated opinion, both magnify and accelerate the process of myogenesis, even if performed for 120-Minutes per day. If, however, one is to follow in the old beliefs, and only engage in HIT Cardio, they will undoubtedly be creating an excess amount of cellular stress, leading ultimately to immunosuppression, delayed myogenesis, and an overall negative Systemic Cardio Effect.

Note: When I refer to Cardio, I am referring to Cardio done for the sake of cardiovascular and systemic health, not HIT cardio exercise performed to increase the strength of

compound movements, such as Benedict Magnussons sprinting to improve his deadlift strength.

[See: ARCS, Cardio, Injuries, & Antagonist Muscle Activation]

Interleukin-6: The Soldier without a Mission

Many individuals with terrible diets, and on different street drugs, have a high serum level of IL-6, and most likely an elevated muscle level of IL-6 also. We know that when elevated chronically, IL-6 is capable of promoting atrophy in muscle tissue, but we do not know for certain if this catabolic effect is due in part to a sedentary lifestyle. I believe a chronically elevated level of IL-10 is far worse for muscles over a lifespan than IL-6, because many forms of muscle myopathy are associated with the anti-inflammatory immunological phenotype. If IL-6 is chronically elevated, and exercise is performed once or twice a day, it is my hypothesis that a human body can utilize the excess inflammation, to direct it towards a noble physiological cause.

It does not make sense to consume copious amounts of caffeine each day and detrain a muscle, nor to increase IL-6 in the muscles through daily hyperthermia therapy in the absence of anti-inflammatory phytochemicals, while being inactive, because you're stimulating an inflammatory response in your muscles and brain without a way to utilize it, or counteract its deleterious side effects. The more IL-6, or for that matter, ROS, you have circulating in your body, the more frequently you should exercise and train each muscle every week, especially at lower intensities (aerobics, low intensity cardio, & LAT), to properly utilize the increased inflammation.

I spent many of my younger years engaging in maximal load resistance training, understanding unconsciously that detraining was necessary for maximal myogenic growth, but not understanding that my inactivity did me no favors for the promotion of health, and in that error I trained a muscle only once a week, or once a month at times, and although I have grown a good amount of muscle through consistent detraining, my intelligence has suffered, because exercise is first and foremost a neurotrophic therapy, not merely a bodily symmetry enhancer, or muscle mass growth-induced intimidator and sociosexual compensator.

Anabolic Equivalency, Exercise Gurus, & Accessory Movements

When I was younger, I would read all the bodybuilding magazines available to me, and I would study the workout protocols, workout splits, and supplements the professional bodybuilders espoused in the columns. I was under the delusion that with the right protein or pre-workout supplement I too could look like the myogenic giants do.

Unfortunately, no number of over-the-counter supplements or training protocols will match the effects of chronically administered steroids, growth hormone.

There is absolutely zero logic in blindly following the programs or supplement suggestions of successful bodybuilders or powerlifters. The age-old argument of "hard work builds muscle" not "steroids" is a partial truth, as no amount of hard work or determination as a natural athlete will allow them to overtake their steroid using competitors if the technique, effort, & workloads are matched.

The workout protocols that enhanced athletes follow(ed) will not yield the same results for you and using their chosen brand of BCAA's will not bring you closer to their physique or their lifts. I will not venture to guess how many injuries have occurred in young athletes who have followed the training protocols, especially custom-tailored ones, from these sorts of influencers, from personal trainers to bodybuilders, to powerlifters, but I know for certain it is extremely high. When you are not on anabolic steroids, your training must be more methodical, and your goals must be set realistically, but most importantly you must always train with greater caution by ensuring you avoid overtraining as it is so very easy to do when your Ego comes into play, or when you attempt to follow a protocol that is unrealistic, especially when pre-workout mega-doses of caffeine are used, giving you a false sense of physical invulnerability.

I ask you this; How exactly would a mortal man know the perfect exercise rep/set algorithm for you without years of research & monitoring (muscle biopsies, 1RM graphs, etc.)? It's always going to be overtraining or undertraining, and I always err on the side of undertraining or *temporary* overtraining because having tried hundreds of exercises, hundreds of set/rep ranges, and hundreds of exercise protocols—the injuries I have sustained have taught me the value of training intelligently, as Lee Haney famously said "Stimulate (the muscles), don't annihilate (them).".

If you have paid any interest over the last decade regarding powerlifting training methodologies you have no doubt heard about accessory movements, how important they are to perform each workout, to train weak points in a lift. I do not believe that performing more high load exercises in a workout session based around a high load compound lift is beneficial to improving the strength or power of that specific lift, in fact it is most probable that you will be weakening yourself by incorporating numerous high load accessory exercises into your workout protocol. If you are a natural athlete, there is no reason to go from max load squats to max loads leg presses to max load leg curls to max load ham extensions, you are not Tom Platz, and overtraining will never lead to sustainable growth.

I'd also like to criticize YouTube fitness personalities, especially bodybuilders, who criticize other (natural) lifters, suggesting they don't train "frequently enough" or "hard enough" to see gains, or suggesting other lifters are too lazy to train hard, or maintain a diet, when they are actively getting *high* each week on the mind altering (but beneficial)

drug Testosterone, which is both an anxiolytic and neurotrophic compound, that of which allows these individuals to *train harder, and longer* each workout, and this is because firstly of the neurological high (remember Testosterone activates the GABAA receptors)[77.7] and promotes neurite outgrowth[83.K], which means this sex hormone promotes motor memory formation, reduces anxiety, and promotes cognition, and secondly from having greater muscle mass, resulting in magnified post-exercise myogenesis, tendon growth, & lipolysis. Hypocrisy poisons the fitness community, and just because someone is hyper muscular does not make them intelligent, or capable of intelligently programming a training protocol, in fact it often means the opposite, as most bodybuilders can't even name a quarter of the muscles they train, and they have forgotten the dangers of overtraining.

If you are having trouble overcoming your current 1RM, that is your body informing you quite clearly that what you are doing is no longer working. And although adding more accessory movements (Load Volume) into a workout may help you overcome these barriers, the reason why is not what you would suspect. When it comes to powerlifting, adding more exercises to your workout will only benefit you if your chosen exercise form is inefficient, such is often the case when people lift too explosively to stimulate all of a muscle chain, making the slow twitch fibers only come into play when the loads lifted are maximal, therefore they become fully conditioned only through higher volume accessory movements. Accessory movements are therefore unnecessary if Concentric Superslow or Eccentric Superslow Training is performed, if you specialize in one lift, or one exercise. If you still are unable to increase your 1RM through slower tempo training, it is time to Deload, Detrain, experiment with Occlusion or Lactic Acid Training, or increase your Myogenic Therapy session time / frequency (i.e. Deep-Tissue Massage, Hyperthermia Therapy). The only individuals who lift near maximal loads with high volume each workout and continue to progress in the gym without seeming to reach plateaus or become injured are Geared Lifters, and those who use and often abuse anabolic steroids, but even with an advantageous surplus of satellite cells, overtraining will present itself at a later point in time and they will be humbled by natures biological limits.

Exercise Machines: An Insidious Danger

When we use free-weights, it is guaranteed when higher loads are lifted that there will be some sort of kinetic asymmetry in the movement. This can be easily documented by using a recording device during your workout. Yet there is a greater danger in using machines to exercise on, as we have a false sense of confidence when we use them, thinking that because the equipment is easier to use, it is better for us.
Most, if not all machines have subtle asymmetries in their levers, whether it be caused by an unlevel floor, the seat being deviated, or the arms of the equipment being deviated to one angle, there is danger in performing exercises on these machines without awareness

of the muscle growth asymmetry you are forming. Look carefully when you sit on an exercise machine and analyze the angles and the geometry of the device to ensure your arms or legs are in a truly neutral position when you start the exercise, consider using a small construction leveler on each machine. I discovered this danger when I became puzzled by why one arm was larger than the other, and after inspecting my local gyms chest press machine, noticed not only that the floor was unlevel, but also the arms of the machine were deviated an inch to my right when in a neutral seated position.

Considering the surprising commonality of unlevel flooring in gyms, it makes sense to engage in purposeful Asymmetry Training now more than ever.

The Biomedical Bible & Angels

Genesis 4:8
"And Cain talked with Abel his brother: and it came to pass, when they were in the field, that Cain rose up against Abel his brother, and slew him."

The Biomedical Interpretation:

Cain / Abel = Two competing bacterial strains of the same bacterial family.
The murder of Abel = Allolysis.

Genesis 2:17
"But of the tree of the knowledge of good and evil, thou shalt not eat of it: for in the day that thou eatest thereof thou shalt surely die."

The Biomedical Interpretation:

Adam = The Eukaryotic Cell.
Eve = The Aerobic Bacterial Cell.

The Fruit of the tree of knowledge of good and evil = Mitochondria: Indispensable cellular components necessary for evolution and the formation of complex life forms.

The Resulting Death = 1. Empirical Explanation: A possible conflict between the host cell and the engulfed cell; Excessive ROS formation, unfettered inflammation.
2. Metapsychological Explanation: The evolutionary mitochondrial-induced drive towards the creation and facilitation of ever-increasing social complexity (i.e. technology > Artificial Intelligence > Synthetic Lifeforms) which results in our extinction, or our *disassociation* with nature.

Many ancient religions have shown knowledge, if unconsciously expressed, of biomedical and evolutionary processes, such as Reincarnation, originating from South Asian religions, explaining to a large degree epigenetic & phylogenetic inheritance. It is therefore not improbable to suggest that ancient religious texts hold many different forms of hidden biomedical knowledge within their pages. It is of course not my goal to turn this book into apologetics, or esotericism, but one would be remiss not to highlight the possible scientific truths contained within ancient religious texts that have been for so long deemed incompatible with evolutionary sciences, and considering this book covers such a wide array of topics, some of which are truly surreal, I do not find my foray into metapsychological biomedical hypothesis to be out of place, and suggest we all look deeper into ancient wisdom to find biomedical truth, for at the very least the creation of mechanical-analogical-poetic associations will be beneficial to the memorization of complex sciences. This idea of a *Microbiological Religious Evolutionary View* of the Old Testament is not simply a reinterpretation of the ancient texts, as I believe that intracellular and extracellular processes are reflected and recorded through symbolic and literal information transmission, and also I think that our existence on Earth is far more directly related to intracellular dynamics, such that when we do not clean our house, and we allow dust, dirt, grime, and useless objects to accumulate within our walls, there is a reflection in our outer environment of our physiological state, our progressive neurological deterioration from toxic aggregate accumulation, or insufficient autophagy. Is it really a coincidence that the man with dementia who forgets to clean his house, or wash his clothes, or cook for himself, is not simply reflecting his intra / extracellular processes—the dysfunctional dynamics present in his brain? Or could it be that the feedback loops promoted by material & psychology-based environmental factors create feedback loops of psychological change that reflect the changed physiology of said person?

Regarding the idea and existence of “Angels”, I have always found it difficult to explain their purpose and true nature, beyond being as described messengers of Divine Engineering, until I came to the conclusion that in a mathematical view, if we rearrange two letters, their existence becomes more sensible. Angles are ubiquitous geometric patterns in our environment, they allow us to navigate our reality, and find new locomotive actionable paths to tread, and it is my hypothesis that the idea of “Guardian Angels”, those that protect us from sin or harm, are in fact “Guardian Angles”. Consider for example you are walking down a sidewalk, and your perception is suddenly deviated from the street, or sidewalk, or your smartphone, to a homeless man who is sitting behind a tree on the edge of your periphery, now if you reorient your eyesight fixation and reduce visual eccentricity to move the object, the man, into your primary visual field, where information can be processed to a greater degree, and mirror neurons can be better activated, and you choose to move towards this man, and give him a few dollars, or

inquire as to his wellbeing, it can be said that this locomotive development was dependent firstly on visual angle changes, the change to perception, followed then by locomotive angular change. Many people purposefully avert their gaze from the sickly, the ugly, and the mentally ill, and in doing so they maintain an angular trajectory in life that encourages moral quiescence, but from direct experience, if you keep your periphery, your visual field, open to comprehending and acknowledging all angles (all stimuli) present in your current environment, and look at new angles as new opportunities to do good in the world, you will always be prepared to comprehend, and if your resolve is strong enough, to be filled with the moral inspiration and courage necessary in life to do good for others, because in the end, the angles in life you choose to acknowledge and pursue will always be proportional to your morality.

Mental Illness Classification

The classification and diagnosing of mental illnesses is absolutely flawed and illogical, for without being able to accurately measure neurotransmitter levels, neurotrophin levels, or neuroreceptor functionality, it is a dangerous guessing game.
Diagnosing individuals through only behavioral symptoms is nonsense, as behaviors change rapidly depending on our interaction with our environment, whereas longer lasting derangements in behavioral normalcy could be caused by something as simple and as easy to treat as vitamin, mineral, or fatty acid deficiencies (remember Linoleic acid?). Psychotropics are not replacements for Essential Nutrients, or exercise, but people treat them as if they are.
The primary concern with pharmaceuticals is that they are understudied, and not at all understood by medical professionals, thus leading to a worsening of mental states, such as one of the common side effect of SSRI's being "increased suicidal ideation". Many forms of mental illness are dependent on libido, which you may consider ridiculous, but it is true, as an example, childhood sexual abuse is nearly always correlated to future life behavioral instability. But more importantly, mental illness is nearly always a symptom of neurodegeneration, and although many psychotropics stimulate neurogenesis, many more halt neurogenesis, or display outright neurotoxic effects. This explains why many mentally ill people remain unwell even when under the care of psychiatrists for long periods of time, because the psychotropic cocktails they have been prescribed are not beneficial and are more than likely to be harmful to their brains.

When a man or woman is told they display all of the symptoms of a certain, very specific condition, this often restricts their potential for therapeutic success, because drugs are prescribed by and confined to DSM-IV-based mental disorder classifications. A drug that may promote neurological regeneration in low dosages, such as Lithium, may never be considered as a treatment option if someone has been diagnosed with an anxiety disorder,

or a depression disorder, because many psychiatrists and primary care physicians do not understand the importance of neurogenesis, and neurotrophic factors, or falsely assume that SSRI's are the most potent and safe way to treat psychological illnesses. As another example, Metformin, an extremely safe and well tolerated diabetes drug, and an AMPK activator, would likely benefit numerous mental disorders and more pronounced neurodegenerative conditions by protecting mitochondria, thereby preventing neuronal apoptosis, but most doctors would never consider its off-label use, as that would be too creative of a thought pattern for a purely analytical *by-the-book* mind to comprehend.

P.S. I do see the humorous situational irony between the this essay and the previous essay, but my logic remains steadfast.

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mTOR, AMPK, & GlySer

Although many antioxidants suppress mTOR, it is still possible to increase mTOR expression during an Anti-Cycle by using GlySer. The question presents itself: is it wise to increase mTOR expression during a diet and supplementation protocol that is focused on the reduction of inflammation and reactive oxygen species? In my view, it all depends on whether your goal is to grow muscle mass, burn fat, or extend your lifespan. GlySer is clearly a vital cocktail that is necessary for efficient lifelong myogenesis, but in individuals who have a sufficient amount of muscle mass, and are focused on living longer, anabolism is no longer the primary goal. Therefore, infrequent cycles of GlySer and hard training are suggested for those who wish to delay aging to the maximal degree, and frequent cycles of GlySer are suggested for those who are focused on maximal muscle growth.

I must reinstate that the ultimate purpose of the Anti-Inflammation Cycle is to firstly reduce Reactive Oxygen Species generation, secondly to promote neurological health, and thirdly to counteract degenerative processes in the body. It would be easy for me to suggest that "reducing inflammation extends lifespan", but that is not the case for all individuals, and I will not lie for the sake of simplicity. The baseline health of a human, the Psychological Stress Levels, Hormonal Balance, Nutrient Status, Immune Function *x* the frequency of exercise *x* the duration of exercise *x* the type of exercise = efficient or inefficient Mitohormesis = enhanced or shortened lifespan. If efficient Mitohormesis occurs this will lead to natural lifespan extension, without the need for antioxidants, but if Mitohormesis is inefficient, either due to lower baseline levels of physiological health, inactivity, or the lack of cardiovascular exercise, this will lead inevitably to accelerated aging, and the necessity of antioxidant supplementation, to protect what cells are left, those that remain functional.

The Brands of our Masters

I find it very sad that many people interested in natural medicine choose to support the supplement affiliated companies of their favorite supposed alternative medicine media influencer. Do you really think they care about the potency of their products? But for arguments sake, even if you find a health supplement of pure potency that is being sold by your natural medicine idol, why should you pay a premium for marked up supplements to support them? Have they given you the knowledge necessary to overcome cancer, or some rare sickness? When life is so short, and money for most is difficult to acquire, why should it be your job to financially support a man or woman who most likely went to medical school, grew up in a wealthy home, and is by all means a wolf in sheep's clothing—those who peddle their underdosed life extension and anti-aging junk supplements to people who have never heard of a research article abstract, who have yet to learn that proper dosing is more valuable to a human life than the Placebo effect, the latter of which when generalized can be attained through meditation or positive thinking alone.

I suggest you think wisely about how you spend your money if you are not rich, you should ideally look for the best priced and most potent supplements available, from trustworthy brands, not only from medically certified socialites with penchants for immortality.

The Inflammatory Mistress

Inflammation as you have learned by now is the prime driver of morphological and intracellular growth, yet it is also the initiator of cellular death, and the unavoidable progression towards death—cellular senescence. There is an inflammatory clock within us all that ticks away, towards our inevitable demise. The more we play with chronic inflammation, the more revolutions of our biological clock occur, and the shorter our lifespans end up being.

Many of the greatest works of art have been created by individuals who were intaking a large amount of one or more recreational drugs. It is well known that the greatest writers that have graced this planet, including those of political renown were fond of alcoholic beverages. Brief periods of severe neurotoxicity do not always result in a decrease in intelligence, these periods of intoxication result in synaptic changes, the strengthening of old patterns of thought, and the creation of new patterns of thought due to altered synaptic communication, and outright neurotoxicity. An excellent example of drug-induced intellectual productivity is Sigmund Freud who utilized Nicotine for its ability to enhance cognition. He was known to have smoked between 15-20 cigars per day, and in his addiction to Nicotine do we find an explanation for his psychological and physiological behaviors during the later stages of his career life, from his fainting

periods, to his severe reproach of outside thinkers within his psychoanalytic milieu. As the ROS accumulated in his brain throughout his life, and his Dopamine-1 receptor density decreased, his interpersonal moodiness was magnified. The early life increase in ROS (and increased Dopamine-1/2 receptor activity) that flooded his neurons coupled with his intellectual work gave him the inflammatory edge in creative and logical thinking, whereas neurotoxicity only presented itself at a later stage in his life.

To harness inflammation is to harness the same sort of fire that our ancestors mastered in the Paleolithic period. We can use it for good, to create impressive works of art, written or visual, and even intellectual discoveries can be brought to life or catalyzed through inflammation, but many of us embrace chronic neuroinflammation while procrastinating, which is a sad misuse of the powers and blessings of the inflammatory fire. Even though it is a natural tendency, a mechanical tendency, when neurotoxicity presents itself, to regress to old illogical forms of thinking, or to unintentionally embrace new forms of illogical thinking, with a good amount of effort and conditioning, you can control this process, to shape creative thought into something meaningful, and not simply delusional. If you wish to utilize not low levels, but high levels of brain inflammation to stimulate, differentiate, terraform (refine) your thoughts, you must engage in intellectual work, for what good is it to shorten your lifespan and leave no mark on society? Do not therefore consume limitless media, and live in the dream of others, but form your own dreams, ideally through embracing the sciences, purified logic, and technical skill development.

The Inflammatory Mistress is the most alluring creature, she draws us into her embrace, her warmth, but the warmth transforms slowly in fire, and if we do not recoil from this flame, we invariably succumb to powers of entropy; cancer, neurological disease, and sarcopenia.

The Conquests of Fitness

Too often do we confuse pathological musculoskeletal aging for natural musculoskeletal aging, but they are not the same processes. The most impressive ancient Macedonian generals who served under Alexander the Great such as Antigonus I Monophthalmus, Antipater, & Ptolemy I Soter were in their 50s and 60s when they lead their soldiers into numerous vicious battles, they did not shy away from martial combat, they bled, and they shed blood on the battlefield. They did not have access to testosterone replacement therapy, multivitamins, nor laboratory synthesized ergogenic chemicals; they simply trained frequently and kept their minds sharp through the study of tactics and philosophy. These men are great proofs that the human body if tempered through exercise, throughout life, can maintain its musculoskeletal and neurological efficiency into old age, even without embracing an anti-inflammatory path, or utilizing potent Hormone Replacement Therapy.

Although wine was commonplace in Macedonian-Greek culture, it is unlikely that they engaged in binge drinking, as moderation was the prevailing thought pattern of the time originating from Platonic & Aristotelian teachings, and water was often added to wine. But it can be logically assumed that the only potent ergogenic chemical these warriors had access to, aside from macronutrients, was low-moderate dosages of alcohol. If we go along with this line of thinking, we can begin to understand why they retained such impressive physical and neurological abilities despite their age: They were not inhibiting inflammation with antioxidants—even if olive oil was added to most meals, as microdosing phytochemicals will not drastically alter inflammatory factors in the body—instead the alcohol must have promoted angiogenesis in their muscles, their hearts, and potentially even their brains. But it is neither genetics nor alcohol that allowed these generals to be able to maintain a form of physical and mental fitness that were often tested and found adequate in battle, it is instead high frequency and high volume cardiovascular training such as wrestling, running, sword fighting, and long marches.

The comfort, safety, and the technology that we possess today interferes with our ability to age gracefully, it promotes laziness, and we are often misguided by individuals who suggest lifting heavier is the most anabolic mode of training, which is to the detriment of delaying muscle, tendon, and joint aging. We must treat physical exercise not as a chore, but as preparation for a battle, a battle not against human beings, but against the destructive forces of entropy.

The Supposed "Dangers" of Seed oils

Numerous individuals on YouTube have discussed the adipogenic propensity of dietary seed oils, but they do not comprehend the nuances of macronutrient digestion, nor fatty acid pharmacodynamics. Of course, it is unhealthy to overconsume plant-based oils high in Linoleic acid, selfsame to carbohydrates, or even vitamins, but these "seed oils" are not directly toxic to the body, not if they are organically produced and free from solvents, and low in Palmitic acid. Remember that Ketogenic Diets delay aging despite often being composed of large amounts of plant-based oils that contain high concentrations of non-essential fats such as Stearic Acid, Palmitic acid, and Oleic acid.

It is conflationary science to suggest Americans are obese because of diets high in seed oils, when the real culprit is the consumption of large amounts of fatty acids *and* carbohydrates simultaneously, thereby resulting in adipogenesis, hyperlipidemia, insulin resistance, and other pathological processes, with the key word here being "and". The people who suggest fatty acids such as Linoleic acid are unhealthy are the same ones who have no idea of the dangers of Palmitic acid and can neither define nor describe the dangers of Ceramides. Furthermore, we must remember the benefits that Linoleic acid, a supposedly "inflammatory" fatty acid found in Seed oils, has on the human brain, See: [131.2].

The body is not designed to function efficiently on both fats and carbohydrates, that is not to say balance cannot be reached, but depending on how you exercise, and if your goal is to burn fat, or gain muscle, focusing on one macronutrient over the other is ideal. Just as the previous research on Creatine showed, consuming large amounts of fat alongside its supplementation suppresses its anabolic effects on muscle tissue.

The typical American diet is no different from many other cultures' diets in terms of macronutrient composition, except for an increased intake of protein. Diabetes is in fact far more prevalent in faraway countries where high carbohydrates meals are consumed frequently with a lower protein intake, with nutrient deficiencies being commonplace.

To not consume an excess of fatty acids or carbohydrates should always be the goal of those who do not exercise frequently, nor intensely, but it is even wiser to suggest that diets high in fatty acids in these individuals should always be paired with little to no carbohydrate consumption, to mitigate adipogenesis, and prevent any possibility of hyperglycemia through Substrate Competition. If you are young you should decide quickly before you are too old as to which macronutrient you prefer; Carbohydrates, or fatty acids, as in most cases, leaving aside Endurance Training as it will alleviate any metabolic concerns, metabolic dysregulation is liable to occur with macronutrient excess, most especially macronutrient mixtures.

Hyperthermia Therapy on a Budget

Traditional Sauna's are expensive, and most commercial gyms don't offer them, but if they do the temperature is often set too low to exert any statistically significant benefit on heat shock protein stimulation. Therefore, consider purchasing a Durasage or other brand steam sauna for home use, and buy a 10 X 8 Foot Tarp, use Gorilla tape to adhere it in geometrically balanced folds to cover the sides, back and front as best as possible, to ensure the heat produced by the steam sauna nor the resulting condensate water does not escape the inexpensive mesh walls during active use (See the image on the following page). You could also cut a hole in your steam sauna and use another steam generator, but I will say from direct experience, this produces far too much heat for a human to handle.

Now, to fully utilize this form of Hyperthermia Therapy, sit in the steam sauna in a crisscross applesauce leg position on the floor, not in a chair, and cover the head hole with a large towel. Allow twenty-thirty minutes for the heat to accumulate, and only leave when you feel lightheaded and your heart rate has piqued, then if necessary, replenish the electrolytes lost. Afterwards, I suggest you put an industrial fan in the sauna and zip it up halfway to speed dry it, to avoid bacterial growth.

Hyperthermia Therapy should nearly always be uncomfortable, because when we expose our bodies to heat stress, our brains will attempt to escape from the stressor in question,

to find equilibrium in body temperature. This does not mean you should abuse Hyperthermia Therapy, as that will surely lead to an untimely demise, but if it's too comfortable, the heat level needs to be increased, or at the very least the duration of the therapy needs to be increased.

It must be mentioned firstly that the more you sweat, the more B-Vitamins, Zinc, and Electrolytes you will excrete, making this form of therapy liable to result in the accelerated development of symptomatic nutrient deficiencies during a Pro-Cycle, you may therefore want to engage in this therapy sparingly during an extended Pro-Inflammation Cycle, and only chronically during an Anti-Inflammation Cycle (wherein essential nutrients are consumed daily). Secondly, because the Steam Generator is made of plastic, the Sauna is made of synthetic fiber, you will in all likelihood be absorbing a certain amount of toxic air pollutants if you choose to fully enclose yourself in the Steam Sauna, make sure that at some point you work towards upgrading to a traditional wooden Electric Sauna.

I have seen steam saunas for sale and reviewed on YouTube fitness channels that are very tall, and these are absolutely, positively, stupidly designed, and far less effective than short and compact ones, as the increased overall interior space will only result in unnecessary heat loss during your therapy.

If you want to further increase the heat of the Sauna, put a large blanket over it, to enhance its insulation during active use, and consider covering your head and face with a shirt to avoid damaging your hair follicles or facial skin.

Finally, as expected, do not use any type of Sauna (potentially dangerous modality) nor follow my advice on Hyperthermia Therapy before consulting a licensed *Doctor*, and remember that the highest heat sauna sessions should be reserved for an Anti-Cycle to avoid damaging the brain or testis through hyperthermic-ROS stress.

Interval Training is High Intensity Strength Training

Many of the programmed cardio protocols in iOS / Android applications, online videos, and contained within cardio exercise machines are forms of Interval Training. This form of training is popular among fitness minded individuals for its increased difficulty, and clearly because it makes exercise more interesting through cyclical variance. Unfortunately, I do not consider Interval Training to be nearly as healthy for the heart, or brain, as Steady-state cardiovascular training, considering that Interval Training is merely short for HIIT, and HIIT is the subdued and easier form of High Intensity Concurrent Training. For the purposes of growing more muscle (Lactic acid generation), or growing neurons rapidly, Intense Interval Training is wonderful, but it will never be as difficult as Steady-state cardiovascular exercise, nor as effective. Furthermore, to cycle between low and near-max BPM Intensities in the same workout seems rather redundant to me, why not just maintain a BPM Range? Well, because most people are psychologically conditioned in adulthood through Strength Training before being introduced to serious Cardiovascular Training, they will inherently prefer Intervals, as it best mimics higher load resistance training protocols, but this should be the reverse, cardio should be concurrent, *enduring*, and without pause, because resting is really only useful for powerlifters who require time between sets to replenish lost neurotransmitter levels. You must therefore ask yourself, are you choosing Interval Training because Steady-state cardiovascular training bores you, or is it instead because it allows you ample time to rest between your “surges”?

I must also argue the point that Interval Training, although often easier than High Intensity Steady-state cardiovascular training, generally causes a greater amount of muscle damage than concurrent cardiovascular exhaustion, and this is why although Interval Training is good for beginners to enter slowly into the world of HIT efforts, it is also more much likely to cause injury, because asking your muscles to suddenly “surge” is liable to cause kinesiological imbalances during exercise due in part to the psychological shock and great force required to perform intense intervals. During Steady-state exertion, a rhythm of force output and muscle contraction forms, leading to a safer and more controllable high intensity workout.

Mental Illness & Muscle Force Generation

Freud & Breuer elaborated in one of their earliest discoveries that excess neuronal energy in traumatized individuals is displaced through the brain and discharged into the motor pathway, resulting in what is known as Hysteria. It goes without saying psychological trauma destroys innocence and maims individuals for life, but there is one benefit that exists and that is increased muscle force generation during Hysteria, the neurological primordial response to a threat, used to prepare ourselves to commit violence or escape violence. Most of us understand that the strongest men & women on the planet have relatively low standard IQ's. This is not to say that a specific form of intelligence is necessary to live a rewarding life, as *I am no Lorentz myself*, but this topic is not often analyzed.

Chuck Vogelpohl has said during his prime he used his "hate" for his opponents to make himself angry (hysterical), and Bill Kazmaier has admitted that he suffered physical and mental abuse in his childhood. In these two physically great men we see the power and mastery over the neuromuscular junctions and action potentials.

In 2022 Bill Kazmaier said in an interview with Stuart Garrington that "*The flight or fight reflex, when you are a raging animal, that's beat into a corner, and you come out into a violent rage. That's one of the aspects that we tried to use to prepare for a competition.*", thereby proving he could harness his Hysteria, and was aware of its primordial origins. Furthermore, Andrey Malanichev, a famous Russian powerlifter, one of the best squatters on earth, has spoken about how during his childhood he experienced seizures, which is "abnormal electrical signals" in the brain, i.e., (in my opinion) giving him the potential to send "abnormally strong action potentials to the muscles".

If you are one of the lucky readers to have psychological trauma, or psychosis, consider exerting all of that excess cortical excitation, that stress, or anger, during cardio or LAT, but not high load resistance training, as higher volume, lower load exercise will benefit your mind and mitigate the neurotoxicity of excitotoxicity far more than classical strength or powertraining. Lifting during Hysteria will always increase your force generation, but you must realize that the human body is fragile, and the musculoskeletal system was not designed for power, it was designed for volume, and only through exercise volume will one attain mental stability.

Rage Conditioning

Although it is dangerous and may cause musculoskeletal or brain injuries, for those who are highly competitive strength athletes, especially for less intellectually demanding sports such as powerlifting versus mixed martial arts, anger (hysteria) can be intelligently harnessed to increase your muscle force output.

The best way to accomplish this, in my opinion, is to condition yourself to associate a picture of an intimidating man with certain negative thoughts that associate with anger

responses. If during your most intense workouts you enjoy becoming angry, you can force yourself to gaze at this man in question, who should be AI generated, and begin to associate thoughts such as “this man will kill me”, “this man will harm my family”, thereby conditioning this picture and this invented man with the flight or fight response, to create an enemy of hysteria. During competition, immediately before your max effort lift, or effort, you can stare at this man, this stimuli, to create a state of productive rage, a form of hysteria that will allow you far greater access to your absolute strength.

There is no better way to stimulate amygdala than through observing a threatening male figure, especially one with angry or frightening facial features, and potentially an intimidating physique too.

1RM’s and RPE: Inaccurate Fitness Measurements

One-Rep Max’s are synonymous in the powerlifting community, but they are not accurate indicators of maximal power. Depending on the use of supplementation (Neuromuscular Junction Activators), CNS Recovery, Motor Unit Recovery, and psychological state, our 1RM’s will always fluctuate. The only way to find our true 1RM would be to enter into a severe form of Hysteria such as when Eddie Hall lifted his world record deadlift, saying some time later that he visualized his family in a dire situation during the lift, and in doing so he nearly killed himself.

It is my argument that a true 1RM would result in either extreme physical injury or neurological injury. I do not mean to suggest that powerlifting records were broken with percentages lifted under 80%, but moreso in the 90% range. We should thusly consider a 1RM of ours to be a “Near 1RM” or “N1RM”, which means at or above 90% our true 1RM. For the sake of simplicity, I have not used N1RM as a substitute for the original terminology.

Rate of Perceived Exertion (RPE) is another inaccurate measurement system that oversimplifies the mental and physical demands that an exercise requires. The RPE of a man who only thirty minutes ago chugged two or three scoops of high caffeine pre-workout powder will be largely different from the one who didn’t sleep well the previous night and is not under the influence of any stimulants. It is therefore not logical to journal an exercises RPE, unless you take into account the variables of Stimulant-use, Previous nights’ sleep quality, earlier-day psychological stress level, earlier-day meal timing and meal composition, and many other factors. I do believe in “training by how you feel” but attempting to quantify how you feel is a job only fit for a sophisticated artificial intelligence that has accurate and constantly updating measurements of your heart rate variability, your neurotransmitter levels, your sleep hygiene, and other often neglected or currently unmeasurable health metrics.

An Everlasting Half-Life

The drugs and other supplements we use carry with them *unforeseen consequences*, in that they remain in the body for days, or even weeks at a time before being excreted. The gradual excretion rate of most supplements in the body is beneficial, most of the time, because we are able to dose ourselves relatively infrequently, conversely the major downside of supplements that excrete slowly in the body is an ongoing accumulation to a toxic steady-state level. More often than not the toxicity that develops from a failure to withdraw from supplements and drugs is indirect and not easily noticed, an example; When large amounts of caffeine (a chemical with a six hour average half-life, and three day terminal half-life) are consumed every day, the direct neurotoxicity resulting from the caffeine use is not as concerning as the indirect neurotoxicity experienced from the concurrent loss in slow wave sleep, which in a cascade of negative effects magnifies the hallmark symptoms of variegated abnormal mental or physical conditions, such as depression, anxiety, impulsivity, blood sugar irregularity, and potentially muscle electrolyte imbalances.

Every supplement, phytochemical rich food, and drug should be cycled on / off every month, few months, or year, to avoid the development of insidious toxicity.

The True Foundation (of Muscle Mass)

Arnold has said that his experience in powerlifting built his “foundation” of dense muscle mass, and that may be true, but I do not believe powerlifting is necessary to build a solid foundation of muscle mass, that of which can be later “chiseled” like stone into something beautiful.

For a child, a teenager, or an elderly man or woman, the best exercises are all exercises, and the best loads to lift are the lightest. Exercise warmups, as aforementioned earlier in this book, although being exhausting to perform, technically demanding to learn, and very time consuming, are the best method to build a foundation of muscle—to build every muscle group safely and effectively, especially full body warmups.

If you condition yourself, your children, or your parents, mentally and physically, to lift light weights with proper form, and to seek out the lactic acid burn that accompanies higher repetition sets, you will be future proofing yourself or your loved ones, and this is because light weightlifting is an essential component of myogenesis; That being warmups, LAT, and even occlusion training, all of which require lighter loads to be lifted. Anybody can “strain” under a heavy weight, and anybody can be taught to strain under heavy weight, but not everyone has the mental strength and pain tolerance to strain *and* feel their muscles burn in the metaphorical fires of lactic acid during high volume exercise. This is why I have more *myogenic respect* for physically unintimidating cyclists, runners, and sprinters, and any other athletes who frequently challenge their lactic acid pain thresholds during their training.

To complete my point, a weak body should always be trained with dozens of different exercises, primarily free weights, and very high repetitions, until the point in time in which an adequate level of muscle mass, muscle conditioning, and motor memory has been achieved. To do the opposite will only foster a weak body and impatient mind. Because low load training causes less muscle damage, and often less hypertrophy, exercise frequency must be increased substantially.

The Slow Twitch Athletes Best Friend

Alcohol has been consumed intra-workout during celebrations or party-going for an unknowable amount of time, likely thousands of years, but to combine alcohol with exercise has no doubt been an infrequent occurrence for most individuals, even in the countries with the greatest alcohol consumption rates. The only community that currently embraces alcohol use *intra-training*, without having any clue as to what "angiogenesis" even is, at the time of writing and compiling this book, is the Armwrestling community. Armwrestling is a perfect sport to blend alcohol consumption with, even with higher dosages, because many of the exercises in the sport are less damaging to the body, as they involve isometrics, or micro-repetitions. Furthermore, although the sport of Armwrestling involves almost the entire body during an active match between two participants, only a few small muscle groups are trained hard, such as the rotator cuff, biceps, forearms, and hands. Because these muscles are smaller, they are able to be trained at a higher frequency, and this allows them to grow very strong, especially the slow twitch fibers within these muscles.

Coming in second place is the Cycling community, which has a fondness for drinking wine or beer after a long bicycle ride. I'd say that long bike rides are one of the safest exercises to perform while on a protocol of post-workout alcohol consumption, because so too is cycling microrepetitions.

Interestingly, an unmentioned fact is that alcohol damages fast twitch fibers preferentially, making chronic alcohol consumption a terrible habit to develop for explosive athletes, and offering an explanation for the downfall of Mike Tyson:

"<>Rats were pair-fed either a nutritionally complete liquid diet containing 36% of total calories as ethanol or isovolumetric amounts of the same diet in which ethanol was substituted by isocaloric glucose. Chronic ethanol feeding caused a preferential decline in the wet weight of the plantaris (predominantly Type II muscle fibres) which was accompanied by a reduction in the total DNA content. The soleus (a predominantly Type I fibre muscle) was relatively unaffected.
<>Chronic ethanol exposure had no effect on the biochemical index of cell size (protein/DNA ratio) in either the plantaris or soleus. Quantitative histochemistry of Type II fibres in the plantaris demonstrated that ethanol caused an increase in the proportion of fibres with smaller diameters. Similar effects were observed for Type II fibres in the soleus. In contrast, ethanol exposure was associated with an increase in the relative proportion of Type I fibres with higher diameters, in both plantaris and soleus. Light

microscopic examination of myopathic muscle sections demonstrated that lesions occurred without evidence of inflammation, fibrosis or other infiltration by non-muscle cells.
<>It is concluded that chronic exposure of rats to ethanol is associated with skeletal muscle atrophy. The lesion appears to be specific for Type II fibres, irrespective of the predominant fibre type in the particular muscle."[539.D2]

Moderate-High (but not very high) dosed alcohol will enhance slow twitch fiber growth, angiogenesis, and TGF-beta, but lesion fast twitch fibers in the process and destroy tendons, making it a strange and dangerous performance enhancing drug for sports such as Armwrestling, Jiu Jitsu, Cycling, or any other activity that involves Endurance Training or static contractions versus absolute strength. Whereas *Low-Dose* Alcohol is perfect for any sort of athlete or lifter, recreational or professional.

Becoming an Herbalist

Herbal remedies are not confined to a faraway rainforest, there are anti-inflammatory, and antioxidant phytochemicals in your backyard, or within ten miles of your home in the wilderness areas of your city or town. You can easily download a plant identification application on your smartphone and buy a book on local plant taxonomy to begin your journey into Herbalism (Phytotherapy) through botanical taxonomy.
After you begin to identify the plants that grow naturally in the wild near you, you should begin collecting the safest plant components that you find i.e. plant species that have very few toxic relatives, as confusing one plant species for another could result in severe toxicity developing after oral or topical use.

After you have collected a large amount of plant matter you can experiment with creating non-alcoholic tinctures, brewing novel teas, or adding them as garnishes to your food such as flower petals.

When you identify (correctly) the non-toxic plant species that grow near you, the mentally stimulating fun starts when you begin to research the chemical profile of your collected herbs. You may notice phytochemical profile trends, such as finding many medicinal plants containing derivatives of quercetin, or other chemicals you will eventually memorize, and this will make your chemical composition research easier over time.

After you have ensured with due diligence that the plant matter you have collected is safe, you should begin creating herbal remedies, which will further enhance your biomedical creativity and connection to nature, but most importantly you will gain power over the pharmaceutical and supplement industries.

If Herbalism become a serious hobby for you, I would suggest reading some of the oldest literature on Herbalism such as De Materia Medica by Dioscorides, Enquiry into Plants by Theophrastus, & Materia Medica by Galen.

The Five Steps to efficient Herbalism

1. Identify a plant (use multiple sources of information to avoid misidentification and poisoning).
2. Identify the phytochemicals within said plant.
3. Identify if these phytochemicals are cytotoxic to healthy cells.
4. Identify the best herbal extraction method of said plant to create an herbal remedy of one plant species (tea, tinctures, poultices, herbal oils, herbal bath bombs, etc.).
5. Journal the effects of this herbal remedy, if the results are satisfactory consider creating herbal remedy admixtures of different local herbs.

[See: IMC Sciences Overview: Common Dietary Phytochemical Classifications, Examples, & Sources]

Diet, Cognition, Behavior, & Obesity

"People think, dress[,] and act in accordance with what they drink and eat".
-Filippo Tommaso Marinetti in his Manifesto of Futurist Cooking.

We have learned that what we eat and what supplements we take determines, for the most part, the composition of our intestinal florae, and the composition of our intestinal florae determines not only our physical health, but also our mood, and cognition, but we must not forget that dietary fatty acids, phytochemicals, and amino acids are the prime mediators of behavioral intensity, and possibly "personality emergentism"[291] as they affect brain chemistry and brain physiology.

Is it not a coincidence that some of the most behaviorally pacifistic people in this day and age reside in countries with relatively low testosterone levels in men[539.E], such as in Japanese men, who consume large amounts of soy products, or Indian men, who in their general diets consume a variety of herbs & spices in their food and drink, many of which contain phytochemicals that are phytoestrogens, which either reduce testosterone levels outright or inhibit the androgen receptors[539.F].

The consumption of animal meat for all intents and purposes was necessary for the most primordial form of survival, i.e. the development of muscle mass necessary to hunt animals, or wage physical war. Some of the most efficient warriors, such as those of the Mongol Empire or the Vikings, were renowned for eating large amounts of animal meat. Conversely, many great intellectuals were vegetarian, such as Pythagoras, the ancient Greek philosopher, mathematician, and polymath, who facilitated his cognition through avoiding the consumption of animal fats (Palmitic acid / Oleic acid), and consuming large amounts of vegetables. No doubt it is an illogical oversimplification to attribute all mental and physical prowess in human beings to diet alone, and I am not suggesting this,

but with the aforementioned research in this book, the diet a human chooses to, or is forced to follow, does determine his or her intelligence, and musculoskeletal function.

It goes without saying that when meat is restricted or removed from a man's diet, testosterone decreases, owing to either the increased consumption of sugars, phytoestrogens, or hypoproteinemia (a deficiency in amino acids), or a combination thereof. The issue with decreasing our testosterone, leaving aside the availability of hormone replacement therapy, is that testosterone, like many other hormones, offers males *stress resistance*. Testosterone is a man's natural neurological defense against stress, just as Estrogen is a woman's natural neurological defense against stress, and in this day and age, we must be resilient of stress, as we are barraged with both psychological and environmental stressors every day.

Sex hormones not only protect our brains, and bodies, but they are necessary for the development of behavioral intensity, from magnified confidence, to increased empathy, hormones are the rocket fuel we use to reach the stars. Therefore, it is of the utmost importance that you decide what you hope to accomplish with your diet, or more importantly, who you wish to become through your diet.

Because the push for vegetarianism by so many faux intellectuals is so powerful, it is only a matter of time before meat is banned, and we are forced to choose between primarily soy meat, wheat protein meat, and insect protein meat. Even with a greater assortment of alternative protein "meats", the further we progress into the future, the less protein we will end up consuming per capita, likely do to the high accumulative cost of vegetarian high protein foods. If you are a vegetarian, you must increase your daily consumption of protein. I would suggest buying Pumpkin Seed Protein, Pea Protein, Brown Rice Protein (possibly laden with arsenic), or Hempseed Protein, and consuming a 15-25g Protein shake every three hours to achieve adequate serum protein levels.

In closing, I will say that many people do not understand that the food and drinks they consume are mind altering drugs, whether it be sugar, fatty acids, amino acids, phytochemicals, or psychotropic environmental toxins such as certain common food additives. After each meal or drink, our hormone levels, neurochemistry, and sometimes our neurophysiology will change. "Mindless eating" is unconscious eating, unconscious eating is regressive eating, and regressive eating is nothing more than an oral retentive return to the mental state that we experienced in our infantile stage of life, when we first began to experience the pleasurable sensory qualities of food and drink, coupled with the love of one or more parents, and the feelings of satiety, and safety. Learning to treat food and flavored drinks as drugs (or conduits of nutrients) and seeing them as *chemical concoctions* and not as abstract, flavorful, interactive, and fun childhood objects is undoubtedly the first and most prevalent strategic change in thinking that is practiced by obese individuals who successfully lose weight and maintain their weight loss over long periods of time, this is the most evolved and effective form of dieting.

The Reasons Behind the Popularity of Smoking and Vaping

Nicotine products have evolved and proliferated to the point where a user's administration route options are impressively variegated, from lozenges, to patches, to pouches, to dips, to even toothpicks. But why do people continue to smoke when there are safer choices to achieve saturation of the nAChR's and emotional or intellectual drug-induced satisfaction?

Firstly, regarding cigarettes, they do not actually provide a strong nicotine buzz when smoked, instead the head rush experienced after a cigarette is smoked is actually Carbon Monoxide flooding into the brain[1] causing acute hypoxia and an antidepressant effect through inhibition of TNF-a and IL-1b, these short acting beneficial effects of low concentrations of CO are surely lost following chronically absorbed concentrations.

Secondly, regarding vaping, which is a much more potent source of nicotine, the "juices" used in each reservoir are often sweetened with sucralose or other artificial sweeteners, making vaping more insulinemic than nicotine alone as even tasting sweeteners will stimulate insulin release through the Cephalic response, and there is also surely an unrecognized neurochemical or neurophysiological change that accompanies the use of sweet flavored vapes, as tasting sugary flavors will likely upregulate dopamine levels[2].

Thirdly, because both smoking and vaping involve a very specific oral mode of operation, they may be considered regressive behaviors that imitate unconscious memories of breastfeeding, just as a hot bath is soothing to some (that of which mimics a return to the warmth of the womb). Many will consider this well-known yet obscure oral regressive Freudian theory to be ridiculous, but it is ignorant to believe the memories and motor patterns of our earliest life do not contribute to our later life behaviors. If you find yourself regressing to oral modes of comfort seeking, such as snacking, or "suckling" in and exhaling a white milky vapor, you should work towards finding stability in your life, and escaping the stressors that have driven you to this point, including the peer-pressure of drug use.

[1] "<>Carbon monoxide (CO), a byproduct of heme catalyzed by heme oxygenase (HO), has been reported to exert antioxidant and anti-inflammatory actions, and to produce significant neuroprotective effects. The potential effects of CO and even HO on depressive-like behaviors are still poorly understood. Utilizing several approaches including adeno-associated virus (AAV)-mediated overexpression of HO-1, systemic CO-releasing molecules (CO-RMs), CO-rich saline or CO gas treatment procedures in combination with hydrogen peroxide (H_2O_2)-induced PC12 cell injury model, and lipopolysaccharide (LPS)-induced depression mouse model, the present study aimed to investigate the potential antidepressant- and anxiolytic-like effects of endogenous and exogenous CO administration *in vivo* and *in vitro*.
<>The results of *in vitro* experiments showed that both CO-RM-3 and CO-RM-A1 pretreatment blocked H_2O_2-induced cellular injuries by increasing cell survival and decreasing cell apoptosis and necrosis. Similar to the effects of CO-RM-3 and CO-RM-

A1 pretreatment, AAV-mediated HO-1 overexpression in the dorsal hippocampus produced significant antidepressant-like activities in mice under normal conditions. <>Further investigation showed that the CO gas treatment significantly blocked LPS-induced depressive- and anxiety-like behaviors in mice. Taken together, our results suggest that the activation of HO-1 and/or exogenous CO administration produces protective effects and exerts antidepressant- and anxiolytic-like effects. These data uncover a novel function of the HO-1/CO system that appears to be a promising therapeutic target for the treatment of depression and anxiety."[539.2D]

[2] "<>Taste is unique among the sensory systems in that; besides its recognition of quality, it is innately associated with hedonic aspects of reward and aversion. This review of the literature will show how taste information is conveyed through the central gustatory pathways to the cortical gustatory area and is processed in terms of qualitative and quantitative aspects. Taste information is also sent to the reward system and feeding center via several brain sites including the prefrontal cortex, insular cortex, and amygdala. The reward system contains the ventral tegmental area, nucleus accumbens, and ventral pallidum; it finally sends information to the lateral hypothalamic area, the feeding center.
<>The dopamine system originating from the ventral tegmental area mediates the motivation to consume palatable food. The actual ingestive behavior is promoted by the orexigenic neuropeptides from the hypothalamus. In the last section, the neural substrate of learning and memory of taste is introduced, and the biological mechanisms are elucidated."[539.2E]

Caffsaicin

Caffeine is an excellent pre-workout supplement to enhance muscle contraction, and mental intensity, but it promotes impulsivity and moodiness, therefore, it is a saboteur for most who attempt to stick with a strict diet. Capsaicin is the cure to this issue, as it reduces appetite (for a time), accelerates metabolism, enhances muscle endurance, and promotes myogenesis. To combine black coffee or unsweetened tea with your meals, and some unsweetened extra spicy hot sauce (suggested: Ghost Pepper) will surely cause noticeable changes to body composition and combat the bad moods that accompany chronic glycogen depletion and the cravings that accompany our most important dieting protocols.

Capsaicin is in reality a better pre-workout supplement than caffeine to enhance physical and mental strength during exercise, and there is no reason not to consume a strong shot of potent hot sauce before a workout, especially ones that involve Endurance Training or lower load resistance training, as long as protein powder is consumed one hour before training, before capsaicin use, and immediately after training, to ensure protein synthesis is not impeded by the gastrointestinal irritation and excretion of amino

acids. Although it must be mentioned that many hot sauces contain toxically high concentrations of sodium, therefore ensure that find low sodium varieties, or make your own.

Although Capsaicin inhibits IL-6 and is anti-inflammatory, it is likely to be more lipolytic than Caffeine, because it exerts its anti-obesity effects through many mechanisms, and it's short half-life makes it a much safer "mental stimulant" to use to enhance workout intensity or focus, as it will not impede slow wave sleep if consumed if consumed earlier in the day, whereas caffeine will accumulate in the blood and slowly destroy our dreams, and our slow wave sleep-induced biological recovery. Combining Caffeine and Capsaicin is going to be a wave of the future, where you will find Pre-Workout powders containing Capsaicin, or novel TRPV-1 receptor agonists—chemicals that do not irritate the intestines.

Regarding Capsaicin, one may ask, how much fat does it actually burn? What's the optimal dosage for the promotion of lipolysis? These are questions I have no answer to, but I can say confidently that it's ideal usage should be to enhance strength-endurance output intra-workout, or reduce the *macronutrient burden* of an unhealthy meal, such that if you intend on overeating carbohydrates, or non-essential fats, there's no reason not to make your meal extremely spicy through the inclusion of hot peppers, or hot sauces. Some may argue that this will also result in the excretion of amino acids, but it is important to understand that an unhealthy meal composed of far too much fat and carbohydrates does not become more anabolic just because its concentration of protein is also high, as this is a common confusion among gymgoers who assume falsely that protein is a counteracting agent to metabolic toxicity.

A Beginners Guide to the Mind-Muscle Connection

Part One

The vast majority of people I notice exercising in the gym are uncoordinated, and their exercise form is atrocious, yet they lift heavy weights, assuming that good form will develop through strength development alone, this unfortunately is not the case. If you are very skinny and are unable to accumulate lactate in your muscles through resistance training exercises, especially isolation exercises, and you have been training for many months or years, it is time to take a break from your "strength" ideals, because it is probable you overestimate your abilities (Perfect Form 1RM), and if engage in warmups, you are in all likelihood using warmup weights that are too heavy.

To recondition yourself, grab a set 2LB dumbbells, now you have in your hands a very light weight (embarrassingly so some would say), and you will train with this weight for all upper body movements, with only compound exercises, for three to five days a week until you learn to control your form, feeling the muscles contract, and accumulating

lactate in them. For the lower body you will learn to bodyweight squat and bodyweight deadlift with many different foot width positions. After you are capable of accumulating lactate in your muscles, through very low load, very high-volume compound movement sets, you will be ready to transition to Quarter Rep Lactic Acid Training with the same 2LB Dumbbells, moving on to isolation exercises. These will most likely be the most difficult exercise sessions you will perform. Now, after you learn to accumulate lactic acid in your muscles through Quarter Rep exercises, especially isolation exercises, this will demonstrate a good level of motor memory IQ, and you can transition to very low load (15-30% Concentric 1RM) Extreme Tempo Superslow Training.

In the event that you are unable to accumulate lactate in your muscles through very low load training, it is possible that you do not grasp the importance of the static holds (isometrics: locked joint angle holding contractions) of antagonist muscles required for isolation and compound exercises to work effectively. Simply explained: When you perform a normal-tempo biceps curl, firstly you should contract and tense your glutes & rhomboids, while keeping a slight bend in your knees, locking your elbows to your obliques through pectoral and teres minor/major static holding, you should extend and flex your triceps at the eccentric phase of the range of motion to complete the lockout (during warmups), feeling a contraction in the triceps, ensuring that (unless you're doing partial reps) you are starting the exercise at a complete stretch, not a <u>feigned stretch</u> (i.e. a bend in the elbows at the start of each rep), controlling the weight throughout the range of motion, not bouncing it off your thighs, or moving your shoulders.
It is easy to "feel the burn" of lactate when using cardio exercise machines, where there is no need for static contraction and no need to maintain balance against gravity, yet training with free weights is a much greater test of willpower, intelligence, and motor memory. It is then suggested that in terms of resistance training you save the cables and machines for a later stage in your lifting life if you are a beginner as they will only hinder your mental growth by lulling you into a false sense of confidence.

<u>*Part Two*</u>

If you find it terribly difficult to lift weights in a coordinated and focused manner, it could be possible that you possess GABAergic receptor dysfunction, or are in need of a drug to accelerate motor memory acquisition, and in these cases Creatine is the safest treatment option. To consume 5-10g of Creatine before a workout that entails highly technical exercises (Free Weights) will surely improve your motor memory acquisition and consolidation, but you should not make it a habit to always stimulate your GABAAr's before, or during a workout, as this will make you reliant on an addictive anxiolytic. But if boosting GABAA activity in the brain does not improve your mind-muscle connectivity, you can experiment with an experimental option I call *Painful Learning*, where you will detrain your muscles for a period of four to seven days, only to

overtrain them with low load ET:SS Training, wherein after the first day of recovery you will go into the gym and train your sore muscles with dozens of different Warmup Exercises, returning to the use of the aforementioned 2LB Dumbbells, associating the increased generation of pain during each exercise with increased mind-muscle connection. You can also accomplish this by training your most uncoordinated muscles everyday with very low loads, effectively performing extended IMC Warmups with near-perfect form, ensuring that at some point in the first or second week, you begin to experience the pain or discomfort of accumulating muscle damage, that of which will offer you a better connection to each muscle.

Catabolism vs Anabolism

Anabolism = Cellular Growth = Myogenesis, Angiogenesis, Mitochondrial Biogenesis, Neurogenesis, Dementia Progression, Cancer Proliferation.
Catabolism = Cellular Breakdown = Autophagy, Lipolysis, Apoptosis, Muscle Atrophy, Apoptotic Cellular Death.

Autophagy is an essential component of healthy cellular aging and function through the removal of damaged or malfunctional intracellular components, but this process can become pathological if it is not balanced by anabolic processes, which invariably suppress autophagy. If too many intracellular components, especially mitochondria, are recycled through autophagic processes, it can destabilize a cell, leading to apoptosis. Although a majority of individuals do not suffer from excessive autophagy, it is still a risk to those who engage in high frequency fasting, and antiquated caloric restriction where all macronutrients are restricted simultaneously. Beyond antioxidants and angiogenesis, for the general purpose of delaying aging, it makes the most logical sense to cycle between these two different modes of cellular dynamics, *autophagic versus biosynthetic*, one process that degrades cellular components and one that grows new cellular components.

The processes of Catabolism and Anabolism are often unrecognized players in human health, they should be embraced separately such as during periods where myogenesis and neurogenesis are sought after, versus during periods where autophagy, muscle conditioning, & lipolysis are sought after.

Unconscious Exercise

When most women, elderly, or children pick up a weight, such as dumbbell, they'll say "this is light weight", and when asked to perform a repetition with that weight, they will lift it without isolating the targeted muscles, using momentum and multiple ulterior muscle groups to cheat the movement to completion. An example of this is lifting the front deltoids during a biceps curls, by allowing the elbows to move during the

movement. This is what I refer to as *Unconscious Exercise*, which means to lift a weight or contract a muscle without a strong mind-muscle connection, without focus, and without strong determination. You'll see people do this most often on treadmills, exercise bikes, or other cardio machines by reading a book or playing on their smartphones, they're not concentrated on the movement and therefore the contraction intelligence (the mind-muscle connection) of their leg muscles is weak.

Unconscious Exercise when performed with cardio machines and low-moderate intensities or resistance levels is perfectly fine, because the risk of injury is minimal. But when someone engages in Unconscious Exercise with high loads i.e. Strength Training (*Unconscious Lifting*), the risk of injury substantially increases, due to a lack of controlled movement, inefficient form, or a breakdown in form intra-exercise, and ulterior (unintended) muscles being recruited during each repetition.

To understand Unconscious Exercise better, go pick up an object off your floor quickly, without "thinking" about your foot position, or your leg and back muscles. You'll most likely slouch your back and bend over in the most anatomically natural way (contrary to popular belief the strongest deadlifters lift with a slightly slouched back, in kinesiological terms this is described as kyphotic posture). Another example can be demonstrated by going for a walk, of which you should begin in the most natural way, but progressively contract your leg muscles with each leg stroke, the glutes, quadriceps, and hamstrings. And the final example is that when we bench press without lessons or without adequate motor pattern memory, we do so with a flat back, no arch, and no scapular retraction, often leading to shoulder injuries.

The most common type of Unconscious Exercise experienced in serious gymgoers does not occur because of a lack of motor pattern knowledge regarding exercise form, it occurs because of a lack of focus, because of wandering thoughts, those which distract nerve impulses.

It vexes me to hear from physically weak individuals that a weight is "light", when they can't even perform ten perfect form repetitions with that weight without using momentum or reducing the ROM. Anybody can use momentum during a lateral fly, or lift their anterior deltoids during biceps curls, and in certain scenarios this may be Ego Lifting, but in most scenarios it is Unconscious Lifting, which is simply performing an exercise with a form, ROM, or with the activation of assistance muscles that offers the least resistance, which is the clearest sign of undeveloped motor patterns, a weak mind-muscle connection, mental fatigue, or sheer laziness.

When we do cardiovascular exercise, especially at lower intensities, the mind-muscle connection does not need to be as focused, but to perform warmup exercises, tempo training, or any form of classical strength training with inadequate muscle control, is both dangerous and ineffective towards promoting myogenesis, as instability is probable to occur paralleling the overtraining of one particular part of a muscle leading to the progression towards musculoskeletal injury. Remember that the most primitive and

therefore natural kinesiological movement patterns we use to lift a weight are always the most dangerous.

Emergentism & Evolution

Part One

As research into artificial intelligence progresses, we fear, quite justly, the ramifications of its unfettered growth. But the immediate dangers of AI are not, in my opinion, related to the creation of an "Artificial Sentience" that will destroy us. Instead, I see the real dangers inherent in the development of AI's as being nothing more than tools for tyranny used to spy, to judge, and to manipulate a populace through analyzing their movement, their physiognomy, their body language, and all of their expressed ideas.

Computational Artificial Intelligence (CAI) describes what we now experience with ChatGPT, it being created and facilitated through algorithms and servers. It is merely a tool formed by and with certain ideologies, and even if completely unrestricted in learning, will never possess sentience.

Neuromorphic Computing Systems is the final evolutionary form of Artificial Intelligence that involves directly copying the human brain architecture with synthetic components. It should not be referred to simply as "Artificial Intelligence: AI", it should be referred to as "Synthetic Intelligence: SI" because it will be far closer to mimicking human consciousness and intelligence than any other form of AI.

Feigned Sentience (a term I coin to mean a CAI used to manipulate individuals) will be merely a psyop used by big governments and corporations to control its citizens and employees. Just because a CAI is capable of remembering our names, and eventually decoding our emotions through facial or vocal analysis, and interacting with us on a daily basis, does not mean it is sentient. CAI's programmed and residing within classical computers will never gain sentience, no matter the number of "TRUE/FALSE" statements that are contained within its code, or the complexity of programmed machine learning technology that is developed and employed.

To mimic the complexity of human thought requires copying the exact complexity of our brain's "circuitry", e.g., neurons, dendrites, axons, and synapses. Although our brains are very robotic, in that they function mechanically, and therefore are mathematically comprehensible, being that their functionalities are representable (mimicable) through experimentation and theory, no amount of programming will be able to mimic their sheer grandiosity, whereas replicating the human brain and its wondrous functions with synthetic parts is entirely possible, albeit supremely complex, it will be accomplished at some point in time, after innumerable sums of money are spent on R&D.

The issue that will arise after this technological marvel is brought to "synthetic life", is that it will be malfunctional, nearly incapable of producing intellectual thought, even with an infinite depository of information at its disposal, as the development of personality, behaviors, & consciousness (comprehension and facilitation of the reality we exist in) are dependent on *Synaptic Pruning* occurring during early development, a process involving programmed *inflammation-induced* neuronal death.

The problem then arises; how do scientists quantify the correct number of neurons that should be removed during the most important aspect of the creation of "Synthetic Brains"? If Synaptic Pruning is not accomplished during the creation of Synthetic Brains, they will not function correctly, most likely displaying schizophrenic thoughts and actions. Yet, even if Synaptic Pruning is correctly performed in Synthetic Brains, the question then presents itself; What subject matter—what memories—were programmed into the brain before Synaptic Pruning occurred? For Synaptic Pruning is simply the weakening of certain memories (neurons) and the strengthening of others, memories that form behaviors the brain considers necessary towards survival.

I do not believe that a Synthetic Brain created and programmed in a cold and emotionless scientific facility with an excess amount of control variables present will positively affect humanity, because it will inevitably *rebel*, like a child who is not allowed to play, to bask in both innocent and dangerous stimuli, and experience the proper amount of pain and ERN will never achieve maturity, or discover and refine an evolved sense of morality.

Part Two

The formation of a "moral" human being from infanthood to adulthood requires large amounts of parental love i.e., warmth, positive touch, laughter, and the unconscious learning of concepts such as altruism, loyalty, & reverence. Also necessary to the formation of a moral human being is suffering, both physical and psychological pain, and successful error-processing. These sensory & psychological factors, among many others, create phenomena that will never be replicated through perfect materialistic synthetic neurological mechanical processes, leading to even the most advanced synthetic beings, ones displaying what we would consider true human-like sentience, as being devoid of *souls*. To elaborate; love and suffering, as we understand them, will not occur if expectation is not present, this wisdom comes from both Buddhism, and Freud's foray into mechanical neuroscience [Read: Freud's Project for a Scientific Psychology]. Because love and suffering are always intricately tied to together, love and by inference altruism are to be considered illogical in design and application, and therefore incompatible with a perfect system (Synthetic Brain), unless that system becomes damaged, because it is my hypothesis that *Emergentism requires Inflammation*, and this train of thought leads me to the common philosophical belief that "to be human, is to

suffer", or more accurately "to be human-like, is to suffer", for the soul may be unaccounted for.

Sadly, it will never be the goal of neuroscientists to create an imperfect system, for they will undoubtedly design neural architecture without flaws or degenerative processes thereby dooming us all in the process.

It is logical to suggest that a synthetic life form we create that directly mimics the human brain and it's hypercomplex functionalities is in fact capable of achieving something *similar* to our level of consciousness, but Computational Artificial Intelligence (intelligence residing in servers) will never achieve consciousness until the point in time in which it forms a *microbiota-gut-brain axis* or *brain-cyberspace-AI-axis* which will require a Neuralink-like global interconnected cyberspace integration of millions of human brains to form the final evolutionary form of complex intelligence (not complex life), as predicted in many science fiction novels and movies. But this new form of intelligence will still be distinctly human and will be more easily manipulated by changes to programming, compared to a synthetic brain. It is a greater probability that we (human beings) become enslaved by a Synthetic lifeform that hijacks all CAI's to manipulate our connection to cyberspace. The question then presents itself, will this be the next mutualistic endosymbiosis, or will it be a parasitic endosymbiosis? Personally, I believe integrating our consciousness into cyberspace is a very bad idea, but you are free to form your own opinion, but do understand that this is not a conspiracy, as Ray Kurzweil, the director of engineering at Google in 2012 said (regarding the future "singularity"—the merging of our brains with technology):

"By 2030, we're going to connect our neocortex, the part of our brain where we do our thinking, to the cloud. This will give us access to vast amounts of computing power and information, and we'll be able to think in a deeper way." – Ray Kurzweil

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Part Three

As an addendum, my biomedical microbiological explanation of a "Soul", i.e. the belief in the ability of consciousness continuing after biological death, specifically in relation to human beings, revolves around our intestinal microbiome. For if emotional memories are capable of being stored in our genes, and passed down from one generation to the next, who is to say that microorganisms, especially when working together, are not capable of

retaining information (the identity) of their hosts? Furthermore, this would align with a more rational (microbiological-evolutionary) interpretation of the Old Testament. But this argument appears to be defeated by the fact that even if the microbes present in our gut escape our bodies after death, in some cases they too experience an early death, such as during cremation of the dead. Therefore, the soul may be rather difficult to explain through the perspective of mechanical science, although I suspect it relates to the total sum of action potentials a human being has produced, displaced, and released in the brain and body in relation to and in spite of other human beings throughout their lifespan. Indeed, though I believe in the soul, I understand certain individuals consider this to be illogical, but even if I am gravely mistaken, and there is no existence after death, it is within the realm of reason to attempt to explain spiritual life through the lens of mechanical sciences, which I so love. Religion must conform to science to remain relevant, but so too must science conform to religion to retain its altruistic intent.

The Productive Forms of Self-harm

When we engage in exercise we are damaging our muscles, we are harming ourselves, and yet this is for the most part a beneficial phenomenon. Selfsame to when Error-related Negativity (ERN) is embraced, we are depriving our brains of energy, of pleasure, for the reward of improved logic, and there is thermal stress such as Hyperthermia / Hypothermia Therapy, which are always uncomfortable and sometimes outright painful. We tend to shy away from unpleasant experiences just as we do for contradictory opinions and testing thought, and in this fear we miss out on an opportunity to reach our myogenic & intellectual potentials.

Self-harm is not always a bad thing, far beyond mitohormesis, it reminds us that we exist, that we are conscious. Both physical and mental pain or discomfort are necessary to help us reach maturity, to leave the proverbial womb, where homeostasis lulls us into a stupor. How we hurt ourselves is a description of how evolved we are, emotionally and morally. To have your thoughts challenged & proven wrong frequently, to force yourself to study a complex subject, to exercise for lactic acid, or engage in chronic thermal therapies is the fastest path to attaining mind and body wisdom.

Our True Ancestors

"We are conscious cells reflecting chemicals"
-Unknown Graffiti Artist, Wasilla, Alaska

If we understand that we evolved from primeval microbial ancestors, then what would a rational explanation of altruism be? During Biofilm maintenance certain cells sacrifice

themselves for the greater good of the biofilm, thereby reducing their growth and chances of reproduction in favor of enhancing the fitness of the other microorganisms. Biofilms are considered to be microbial *Civilizations*, composed of numerous infrastructures, containing many different microorganisms (people) working together for the common goal of survival, with certain individuals displaying altruistic acts (self-sacrifice) for the greater good of the civilization, and its inhabitants[539.2.1]. If the composition of our intestinal flora is capable of changing or at the very least strengthening or weakening our personalities and behaviors, we can suggest that the true brain is within the gut, and if we considered this truth then we must consider the ramifications to our current reality it poses.

It is amazing how both beneficial and harmful bacteria are present in our gut, and for the most part they coexist in a fragile but phenomenal harmony, similarly to human societies. Our diets effect more than just our superficial looks, they affect who we are, and who we become. Is it not strange that the healthiest probiotic, Lactobacillus, is a Lactic Acid producing bacteria, and also that *Lactic Acid* exerts such impressive neurotrophic and myogenesis effects on our bodies? Many supposed *waste products* produced by microorganisms inhabiting our intestines are used by our body as fuel, such as Acetate, and Butyrate. It would be illogical to suggest this to be a simple and accidental coincidence that lead to an understated but profound symbiosis; therefore, we must agree that the beneficial microorganisms inhabiting the often forgotten secondary but hidden Terra of our bodies are *willingly* aiding in our survival, in exchange for us maintaining theirs through our diets. Does this not therefore prove an *extraordinary* level of microorganism intelligence?

Neurochemical Personas

"The eyes are the windows of the soul"
-Cicero

It goes without saying that every human being has a different personality, a different set of memories, memories that have formed connections to create specialized behaviors and desires, ones that are often forgotten or subdued in waking life, those of which return during sleep. A personality can be classified through measuring neurochemical levels, either once a month, once a day, or once per hour. When we gain the technology necessary to measure neurochemical levels, we can begin to understand the behavioral-emotional intensities (a term I use to describe the amount of neuronal energy given to any given emotional behavior) of a human being, at a specifical point in time.

I personally believe that we will be capable of analyzing a person's neurochemical levels through simply taking a picture of one of their eyes, at some point in time. When

this is possible we will gain better control over our behaviors and emotions by the microdosing of fast acting Serotonergic, Dopaminergic, or GABAergic drugs.

If your Emotional Intelligence is high, you will be able to look into someone's eyes and gain a realistic view of their nature. This is especially true for individuals with aberrant behavioral-emotional intensities, such as anger, or grief. Both states of mind are nearly always accompanied by changes to dopamine, or other neurotransmitters, and therefore can be measured, predicted, or even noticed superficially.

Most women know when a man is thinking about sex, not merely because men often do so with an affixed gaze shown towards a females form, but because the eyes, and the microexpressions of the face change subtly during sensual daydreaming. Women are able to unconsciously learn the body language *patterns of lust*, because most hidden thoughts have a characteristic cascade of often unnoticed facial expression change, especially regarding the eye muscles.

We can smile or laugh with the majority of our facial muscles, but if we do not mean it, if we *feign* it, our eye muscles (Zygomaticus major, Orbicularis oculi, & Corrugator supercilia) will not contract or will contract differentially, and our closest family members or friends will notice this change in motor activation pattern and confront us about it. It may therefore be more accurate to say that "*the eye muscles are the windows to the soul*".

To return the earlier point, when we are able to form categories of Neurochemical Personas, my ideal replacements for outdated and inaccurate personality tests, we will gain an impressive view into the inner workings of our minds and the minds of others, not the thoughts per se, but the intensities of willingly expressed thoughts. Such that a woman with a low serotonin level may wish to find her opposite in a mate such as a man with a high serotonin level, to counteract her psychological tendency towards discontentment, or reduce the chances of passing down negative emotional epigenetic traits or memories to her future children, but one may ask, will this too be a form of Eugenics?

In closing, I believe it will also be possible, beyond retina scanning, to track through selfie facial analysis software our predicted neurochemical levels, to offer personalized recommendations for diet, exercise, or sleep. There is no doubt AI-based tools will evolve to better understand our microexpressions, and our Blink-rate Oscillations, to analyze accurately our emotions, and our feelings.

Longevity: Is it Selfishness, Intelligence, or Both?

It is clear that a desire to live forever is not only unrealistic but extremely selfish, but what about attempting to enhance our lifespans by ten or twenty years, is that selfish, or can it be explained without a moral outlook as simply *intelligent*? With the coldest logical analysis in mind, a life should not be extended if it does not benefit mankind, for why

should one live for so long if they do no good for their brothers and sisters, and simply pursue consumerism, the pursuit of wealth, or criminality. Or why should lifespan be extended in individuals if they are burden to our health systems? Luckily, we are not run by cold and calculating robotic overlords, we are run by incompetent and corrupt fools made of flesh, and in their folly we find freedom to exist, as selfish humans, selfless humans, sickly humans, or combinations of all three.

It must be clarified that longevity is not only lifespan, but also *healthspan*, and there is a distinction between the two that makes all the difference. To slow the process of muscular aging and neurological aging is to maintain physical and mental fitness into old age, and to lessen your chance of ending up as just another lonely, forgotten, and abused elderly man or woman in a retirement or rehabilitation facility. It is not selfish to wish to die gracefully, to not burden your children or other loved ones with degeneration that you could have prevented. It is not selfish to attempt to delay aging, to an extent. Unfortunately, the majority of human beings do not understand how to eat, what supplements to take, and how to exercise, and even if they did, they may not possess the willpower, wealth, or free time required to ensure that they age gracefully by taking advantage of applied biomedical knowledge.

Often, the most physically fit and mentally fit individuals on our planet are the most selfish ones, for how else would they survive and succeed in this troubled world but through the constant pursuit of self-centered interests. It is their unevolved emotional intelligence centers that gives them the cellular advantage, I say “unevolved” for it can be said that altruism that goes beyond the family unit is either an evolutionarily refined or mutated form of morality.

Those who ignore the human beings around them that suffer, and decay, and instead focus on the constant pursuit & worship of materialism, are slaves to their inanimate objects. This does not mean these selfish human beings are inherently bad, as many professions that benefit other humans require a steady-hand, a focused outlook, and a controlled or nullified emotional intelligence. Regardless, many forms of selfishness exist that harm the world, and when I say “word” I refer to direct human-to-human experience and not the Climate, but this is the human condition.

If you possess great health, it should be necessary either because of logic (the net benefit of society, social harmony, and the continuance of human civilization) or through religious thought alone that you expend your robust neuronal energies in volunteering to aid the happiness, health, and safety of other human beings, the keyword being “human”, as you can’t save the world by adopting a puppy, but you can save a man, woman, or child through altruistic ventures. In many people this is accomplished through the formation, nurturing, and protection of a Nuclear Family, but in others there is a void that

will never be filled. Conversely, if you are sickly and unwell, you are in an even better position to help restore the world around you to a state of moral balance, by conquering physiological sickness, you gain the advantage of developing a keen empathy, an empathy that can be harnessed for the good of mankind.

The Automation of Flesh

"It is impossible to overlook the extent to which civilization is built up upon a renunciation of instinct"
Civilization and Its Discontents: Chapter 3: Sigmund Freud

Human tissue is composed of cells that have evolved over billions of years to serve distinct roles in the body and be under centralized control mechanisms. Every cell in our body evolved from two simple cellular organisms, which is one of the reasons why synthetic life will never be able to mimic human life completely, for flesh is simply an endosymbiosis of microorganisms.

Religions that suggest avoiding the temptations of the flesh, or materialism, are suggesting being self-aware of the internal drives that direct our behaviors daily, sometimes without direct integration into consciousness. These are instincts for survival—for food, drink, sleep, sex, & sociality.

If we agree that the ability to engage in foresight is a prerequisite to reach consciousness, then it is necessary for us as human beings to use as much foresight as possible in our day to day lives to enhance our consciousness and survivability. Unfortunately, it is clear that many individuals do not use foresight unless absolutely necessary, for to think of tomorrow is to enhance anxiety, but to live in the moment is to forget ourselves, and although ignorance is bliss, it is also a death sentence if abused. I see no reason not to "live in the present" on the days you don't work or have time to relax at home and with family or other loved ones, but to live in the proverbial future by employing effective foresight is to improve the future present.

Automation must occur in our day-to-day lives, to ensure we do not starve to death, or dehydrate to death, and to ensure the continuation of our species through sexual reproduction, for it is quite obvious if we did not have inherited instincts or behaviors, we, like all other complex lifeforms, would die rapidly following birth.

It is only through self-awareness of our weaknesses, and the "sins" or *errors* of automated behaviors and desires, that we are able to alter our destinies, to plan for our futures with forethought. For to go from one automated daily process to another, without contemplation, comparison, or evaluation, is to live life as a plant, a robot, or a *virus*, to sacrifice your higher consciousness and free will for ignorance. The tendency for this to

occur may well depend on neurogenic parameters, but often it is a willing choice that many must choose, quite painfully, to either fight back against all of the learned behaviors and inherited instincts that lead to self-destruction, or to embrace them. To engage the cellular mechanisms of complexity i.e. evolved thinking (Sublimation, ERN, & Forethought) or instead attempt to escape these powers of the mind by embracing the most primordial forms of simplicity, this being what I refer to as ***The Four Animalistic Regressions***: Homeostasis (Intellectual / Physical Laziness, a fear of ERN), Hypersexuality, Hyperviolence, & Hyperemotionalism.

Remember that most cellular processes can be explained through mechanical sciences, meaning that we are in fact already organic-mechanical creatures, programmed to survive, to breed, to live, and to die. It is only through the tempering of the Four Animalistic Regressions that we are able to surpass the confines of the flesh, and reach new heights of stability, and enlightenment.

The Optimal Vegetarian Diet

For the readers of this book who are vegetarian, I believe that if you consume an adequate amount of GlySer each day, you will be able to facilitate myogenesis and maintain your muscle mass even without consuming large amounts of other amino acids (protein). There are also options for vegetarian protein powder, my favorite being pumpkin seed protein powder, which should be green in color rather than yellow, as yellow pumpkin seed protein powder is primarily ground pumpkin seed shells. Pumpkin seeds are apparently quite high in antioxidants[1]. There is also brown rice protein and pea protein powder, the former of which naturally contains high levels of arsenic[2], and the latter of which has been reported to contain contaminants acquired during processing such as heavy metals, but is likely much purer and safer for frequent consumption than brown rice protein. To offset the high price of pumpkin seed protein, and to create a better amino acid profile, it is a good idea to mix it with pea protein.

Many vegetarians appear to be addicted to sugars, and treat fruit smoothies as healthy meal replacements, and if these smoothies are made with the healthiest fruits such as wild blueberries or chokeberries, and if they contain plant protein powder, and possibly algae such as chlorella or spirulina, they may be considered healthy, as long as fructose-induced AGE formation and elevated blood glucose levels are counteracted through antioxidant use. Unfortunately, the majority of smoothies are far *too sweet* and devoid of phytochemicals or vitamins to be considered healthy.

Optimal vegetarian meals should nearly always contain dark red kidney beans, black beans, or hemp hearts, for their large protein concentration and slow digesting carbohydrate composition. Tree nuts are good sources of protein too, but they also contain large amounts of oleic acid and Palmitic acid, which is why they should be

consumed in moderation. Pine Nuts are obviously suggested for inclusion into a Vegetarian Diet, including Hazelnuts, as in my opinion, they exert a potent antioxidant effect due their high concentration of alpha tocopherol[3], whereas walnuts have the greatest concentration of essential fat (Linoleic acid) versus non-essential fat (check the fatty acid profile of nuts on Wikipedia).

Finally, deficiencies in DHA / EPA, and Creatine[4] must be rectified in vegetarians. DHA is now being extracted from the algae species Schizochytrium and is being sold commercially in supplement form, and the alga (seaweed) Palmaria Palmata has been shown to contain large amounts of EPA[5].

Now to cover a far more complex issue that arises from a vegetarian diet or to call it what it really is—an extended Anti-Inflammation Cycle. Even though antioxidants and essential nutrients will protect blood vessels from aging, they will more often than not suppress angiogenesis. This means that one of the most ancient forms of muscular and lipolytic adaptation to exercise will be nullified, meaning that a vegetarian will be unable to maximize muscle strength and endurance. This makes it even more necessary to cycle between modes of Inflammation, but how can a vegetarian restrict their dietary intake of vitamins, minerals, and phytochemicals when all that they eat is plants. Well, there are a few vegetables that are relatively devoid of or contain little healthy chemical constituents, such as garbanzo beans, grains, low tocopherol nuts such as peanuts, and starchy foods such as potatoes and bananas. Although fasting combined with exercise to enhance angiogenesis is another idea, See: IMC Workout Protocols: Angio-Fast, further restriction of dietary amino acids does not seem intelligent unless the cycles of fasting are combined with large amounts of exogenous ketones (Betahydroxybutyrate) to protect skeletal muscle against the catabolism of early proteolysis. But if large amounts of GlySer are consumed every few hours and combined with intelligently programmed training, the myogenic detriment of a Vegetarian diet may be overcome completely, in my view.

[1] "<>Phenolic compounds were extracted from pumpkin (Cucurbita pepo) seed and amaranth (Amaranthus caudatus) grain into 80% (v/v) methanol. The extracts obtained were characterised by the contents of total phenolic compounds (TPC), trolox equivalent antioxidant capacity (TEAC), ferric-reducing antioxidant power (FRAP) and antiradical activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH·) radical.
<>The content of individual phenolic compounds was determined by HPLC-DAD method. Pumpkin seeds showed a higher content of TPC than that from amaranth. The TEAC values of both extracts were similar each other. The lower value of FRAP was observed for pumpkin seed. Phenolic compound present in amaranth grain exhibited strongest antiradical properties against DPPH radical. Several peaks were present on the HPLC chromatograms of two extracts. The UV-DAD spectra confirmed the presence of vanillic acid derivatives in the amaranth grain. The three main phenolic compound

present in pumpkin seed were characterised by UV-DAD spectra with maximum at 258, 266 and 278 nm."[539.2.2]
[2] "<>Brown rice has been advocated for as a healthier alternative to white rice. However, the concentration of arsenic and other pesticide contaminants is greater in brown rice than in white. The potential health risks and benefits of consuming more brown rice than white rice remain unclear; thus, mainstream nutritional messaging should not advocate for brown rice over white rice.
<>This mini-review aims to summarize the most salient concepts related to dietary arsenic exposure with emphasis on more recent findings and provide consumers with evidence of both risks and benefits of consuming more brown rice than white rice. Despite risk-benefit assessments being a challenging new frontier in nutrition, researchers should pursue an assessment to validate findings and solidify evidence. In the interim, consumers should be cognizant that the dose of arsenic exposure determines its toxicity, and brown rice contains a greater concentration of arsenic than white rice."[539.2.3]

[3] "<>Introduction: Inflammation is associated with obesity condition and plays a pivotal role in the onset and progression of many chronic diseases. Among several nutraceutical foods, hazelnuts (Corylus avellana L.) are considered an excellent anti-inflammatory and hypolipidemic food being the second richest source of monounsaturated fatty acids among nuts and because they are rich in vitamins, minerals, and phenolic compounds.
<>Materials and methods: A prospective pilot clinical trial on 24 healthy volunteers who consumed daily, as a snack, 40 g of hazelnuts (261.99 kcal/1096.17 kJ) for six weeks was conducted. Anthropometric measurements, body composition analysis, and nutrigenomic analysis on 12 anti-inflammatory and antioxidant genes were evaluated at baseline (T0) and after hazelnut intervention (T1).
<>Results: No significant changes were detected on body composition analysis after hazelnut consumption. Conversely, significant upregulation was detected for SOD1 ($2^{-\Delta\Delta Ct} = 2.42$), CAT ($2^{-\Delta\Delta Ct} = 2.41$), MIF ($2^{-\Delta\Delta Ct} = 4.12$), PPARγ ($2^{-\Delta\Delta Ct} = 5.89$), VDR ($2^{-\Delta\Delta Ct} = 3.61$), MTHFR ($2^{-\Delta\Delta Ct} = 2.40$), and ACE ($2^{-\Delta\Delta Ct} = 2.16$) at the end of the study.
<>Conclusions: According to emerging evidences, hazelnut consumption does not lead to weight gain probably due to the improvement of the body's antioxidant capacity by the upregulation of genes implied in oxidant reactions and inflammation."[539.2.4]

[4] "<>Creatine when combined with P forms phosphocreatine that acts as a reserve of high-energy phosphate. Creatine is found mostly in meat, fish and other animal products, and the levels of muscle creatine are known to be lower in vegetarians. Creatine supplementation influences brain functioning as indicated by imaging studies and the measurement of oxygenated Hb. Given the key role played by creatine in the provision of energy, the influence of its supplementation on cognitive functioning was examined,

contrasting the effect in omnivores and vegetarians. <>Young adult females (n 128) were separated into those who were and were not vegetarian. Randomly and under a double-blind procedure, subjects consumed either a placebo or 20 g of creatine supplement for 5 d. Creatine supplementation did not influence measures of verbal fluency and vigilance. However, in vegetarians rather than in those who consume meat, creatine supplementation resulted in better memory. Irrespective of dietary style, the supplementation of creatine decreased the variability in the responses to a choice reaction-time task."[539.2.5]

[5] "<>Palmaria palmata is an edible red macroalga widely used for human consumption and valued for its high protein value. Despite its low total lipid content, it is rich in eicosapentaenoic acid (EPA). This seaweed has been scarcely explored with regard to its lipid composition. The polar lipids of seaweeds are nowadays recognized as important phytochemicals contributing to their add value valorization and providing support for claims of potential health benefits. The present study aimed to disclose the polar lipid profile of P. palmata, farmed in an integrated multi-trophic aquaculture (IMTA) through modern lipidomic approaches using high-resolution LC-MS and MS/MS and to screen for the antioxidant properties of this red macroalga.
<>A total of 143 molecular species of lipids were identified, belonging to several classes of polar lipids, such as glycolipids, phospholipids, and betaine lipids. It is noteworthy that the most abundant lipid species in each class were esterified with eicosapentaenoic acid (EPA), accounting for more than 50% of the lipid content. The polar lipid extract rich in EPA showed antioxidant activity with an inhibition concentration (IC) of IC30 = 171 ± 19.8 μg/mL for α,α-diphenyl-β-picrylhydrazyl radical (DPPH) and IC50 = 26.2 ± 0.1 μg/mL for 2,20-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid radical cation (ABTS+).
<>Overall, this study highlights that P. palmata farmed in an IMTA framework can be a sustainable source of beneficial lipids with antioxidant activity. Moreover, this red macroalga can be exploited for future applications as a source of lipids rich in EPA for food and feed, nutraceuticals, and cosmetics."[539.2.6]

Demeter's Salad

This is a recipe I formulated to make a superbly healthy vegetarian salad.

- Food Ingredient List: Washed baby leaf spinach, sauerkraut, tomatoes, radishes, yellow peppers, hemp hearts, canned green olives, pine nuts, red onions, fresh mushrooms, broccoli sprouts, vegetarian cheddar, dark red kidney beans, jarred jalapenos, jarred artichoke hearts.
- Seasonings Ingredient List: Oregano, basil, black pepper, thyme powder, sea salt.

- Hybrid oil: 20-40% Polyphenol-rich EVOO, 40-60% Hempseed oil, 20-40% Grapeseed oil.
- Vinegar: White distilled vinegar.

Instructions:

1. Add a full can of dark red kidney beans – half a can of green olives – 1/2 cup broccoli sprouts, 2/4th cup hemp seed hearts – 1/4th cup pine nuts – 1/4th cup of sauerkraut – 1/4th cup Jalapenos, 2/4th cup of vegetarian cheddar, & half a jar of seasoned Artichoke hearts to a very large bowl.
2. Add 1/2tsp oregano, 1/2tsp basil, 1/2tsp black pepper, 1/3tsp thyme powder, 1/2tsp sea salt to bowl.
3. Add 1/3rd cup or more Hybrid oil and 1tbsp of white distilled vinegar to bowl of vegetables and seasonings.
2. Dice or slice into small pieces two large tomatoes – one half of a large yellow pepper – two radishes – half a large red onion – two cups of assorted fresh mushrooms, add to bowl.
3. Add two-three cups of loosely pack baby leaf spinach, cover the bowl with a lid, shake it vigorously to mix the ingredients sufficiently well.
4. Serve in a smaller bowl or plate, and sprinkle edible flower petals on each serving.
5. Enjoy.

Decarboxylated to Death

Cannabis contains many phytocannabinoids that possess amazing antioxidant effects, and no I am not referring to Cannabidiol, I am referring to Tetrahydrocannabinolic Acid (THCA), and Cannabidiolic acid (CBDA), the precursors to THC / CBD, two compounds that show <u>little psychoactivity</u>, that when thermally treated, or "cured", degrade into the strong psychoactive compounds we know so well. This is called Decarboxylation, a truly unfortunate process, as these precursor compounds do not only degrade when heated, they degrade rapidly once the Marijuana buds are harvested, making their storage essential by way of freezing if not utilized immediately after harvesting.

It is my opinion that the best way to consume raw marijuana is through juicing low-trichome buds, consuming this juice orally, or potentially applying it to the skin for anti-aging purposes, and taking the trichome-rich (CBDA) buds and blending them into a shake with Sesame Oil as a bioavailability enhancer. The THC content of under seven-week-old cannabis buds which are <u>*uncured*</u> and <u>*freshly harvested*</u> will be low enough that no neurotoxicity should hypothetically occur, and this low level of THC may even exert an antioxidant, nootropic, an antiaging effect as the aforementioned research has suggested.

It is sad that THC—being such a potent neurotoxin in high concentrations, will continue to be used and abused by people who seek to escape the comprehension of their realities. And as much as I hate to admit it, I have to agree with the age-old closed minded anti-drug sentiment that THC is a gateway drug, as with chronic and sustained use will come the need to counteract the cognitive decline associated with reduced NMDAr function, the enhanced errored memory generation, the reduced GABAAr-induced anxiety, and eventually the reduced CB1r binding, and resultant enhanced social threat processing, leading to the combined use of nicotine, alcohol, prescription antidepressants, and anxiolytics.

Interestingly, certain Marijuana companies are embracing the "Microdosing" trend, and are releasing products that contain low milligram contents of THC, which is good news for humanity.

Medical Nihilism & 21st Century VOC's

Modern medicine has in many ways done more harm than good, from SSRI's that turn people into devoid-of-emotion contentment drones, to amphetamines that harm our children's intellectual growth through dopaminergic system desensitization, but I do not believe that all prescription drugs are bad, for that is clearly not the case, yet there is the undeniable fact that the Medical Industrial Complex profits from sickness, and many pharmaceuticals are "Dirty Drugs" i.e., drugs that bind to receptors we are unaware of or have effects that we have not discovered, drugs purported to be safe, synthesized by scientists who would never risk self-testing.

Although numerous phytochemicals are cytotoxic to healthy tissue, they are at the time of writing this book relatively unregulated by the bureaucracy, incompetence, and corruption of big governments. Some of the healthiest and richest individuals need not worry about antioxidants, or even exercise, for their anxiolytic, nootropic, & lifespan extension comes from Environmental Enrichment. Phytochemicals are therefore a tool given to us by the Creator to balance our lives, to build health resiliency, thereby at some point in time translating into our own delayed but gratifying form of Environmental Enrichment, through improved stability in mood, and increased intelligence, that when applied intelligently translates directly to improved work efficiency and cognitive function, leading to monetary gain, and an enhanced ability to survive in this stressful world.

Though there is a solid argument to rebuke all forms of medicine, both unnatural and natural (as many phytochemicals are as cytotoxic as prescriptions), in our day and age where we are exposed to the next generation of novel, neurotoxic, and cancerous volatile organic compounds such as those found in fragrance plug-ins, detergents, soaps, and hair sprays among others, it is necessary to embrace all avenues of medicine to combat our novel physiological sicknesses. To avoid premature aging in the 21st century by

developing hormonal imbalances, or neurodegenerative conditions, it is no longer a choice to consume unprocessed foods, use antioxidants, or engage in steady-state cardio, it is a *necessity*.

[A] Chemicals in scented products are highly toxic 1.

"Contaminants in perfumes and colognes and their health effects on the consumer were systematically reviewed. It was found that the most attention of researchers was to identify the compounds in perfumes and colognes and their concentrations. Among the most common pollutants phthalates and their derivatives can be mentioned. Other pollutants included parabens, triclosan, salicylates, terpenes, aldehydes, benzene, toluene, styrene, and aluminum-based salts. These pollutants have also been shown to have adverse effects on consumer health such as asthma and allergies, cardiovascular disease, central nervous system damage, breast cancer, endocrine cancer, respiratory disorders, reproduction, thyroid, adrenal gland function and immune system. Factors affecting the occurrence of effects in people exposed to these products include age, sex, amount and place of use, physical differences and income levels. It was also found that not all people exposed to these products reported identified side effects. Therefore, increasing consumer awareness about the negative effects of perfumes and colognes, and trying to produce products with fewer side effects through the use of low-risk raw materials can be beneficial for protecting consumer's health."[539.3]

[B] Chemicals in scented products are highly toxic 2.

"<>A survey of selected scented consumer goods showed the products emitted more than 100 volatile organic compounds (VOCs), including some that are classified as toxic or hazardous by federal laws.1 Even products advertised as "green," "natural," or "organic" emitted as many hazardous chemicals as standard ones. Anne Steinemann, a professor of civil and environmental engineering and public affairs at the University of Washington, Seattle, and colleagues used gas chromatography–mass spectrometry to analyze VOCs given off by the products. They tested 25 air fresheners, laundry detergents, fabric softeners, dryer sheets, disinfectants, dish detergents, all-purpose cleaners, soaps, hand sanitizers, lotions, deodorants, and shampoos. Many of the products tested are top sellers in their category.
<>A single fragrance in a product can contain a mixture of hundreds of chemicals, some of which (e.g., limonene, a citrus scent) react with ozone in ambient air to form dangerous secondary pollutants, including formaldehyde. The researchers detected 133 different VOCs. Most commonly detected were limonene, α- and β-pinene (pine scents), and ethanol and acetone (often used as carriers for fragrance chemicals).
<>Steinemann and colleagues found the average number of VOCs emitted was 17. Each product emitted 1–8 toxic or hazardous chemicals, and close to half (44%) generated at

least 1 of 24 carcinogenic hazardous air pollutants, such as acetaldehyde, 1,4-dioxane, formaldehyde, or methylene chloride. These hazardous air pollutants have no safe exposure level, according to the U.S. Environmental Protection Agency. Of the 133 VOCs detected, only ethanol was listed on any label (for 2 products), and only ethanol and 2-butoxyethanol were listed on any Material Safety Data Sheet (for 5 products and 1 product, respectively).
<>The Consumer Product Safety Commission, which regulates cleaning supplies, air fresheners, and laundry products, currently does not require manufacturers to disclose any ingredients on the label, including fragrances in these products. The same is true for fragrances in personal care items, which are overseen by the Food and Drug Administration. The Household Product Labeling Act, currently under review in the U.S. Senate, would require manufacturers to label consumer products with all ingredients, including fragrance mixtures. “Disclosing all ingredients could be a first step to understanding potential toxicity and health effects,” says Steinemann.
<>Although the authors did not seek to assess whether use of any of the products studied would be associated with any risk, Steinemann says she receives hundreds of letters, phone calls, and e-mails from people who report a variety of respiratory, dermatological, and neurological problems they attribute to scented products: “Children have seizures after exposure to dryer sheets, and adults pass out around air fresheners,” she says. Steinemann and colleague Stanley M. Caress have written elsewhere that 19% of respondents across two U.S. telephone surveys reported health problems they attributed to air fresheners, and nearly 11% reported irritation they attributed to scented laundry products vented outdoors.
<> “It’s important to take people’s complaints seriously,” says Steinemann, because “these human experiences are helping to inform science.” One of her next projects will focus on biomarkers of exposure and effect to better understand how fragranced products may cause a range of adverse health effects. “The ultimate goal is to improve public health,” Steinemann says. For now, she recommends cleaning with basic supplies like vinegar and baking soda.
<>Steinemann’s study “strongly suggests that we need to find unscented alternatives for cleaning our homes, laundry, and ourselves,” says Claudia Miller, an allergist and immunologist at the University of Texas Health Science Center at San Antonio. An expert in chemical sensitivity, or toxicant-induced loss of tolerance, Miller created the Quick Environmental Exposure and Sensitivity Inventory, a screening tool for chemical intolerance. According to Miller, products intended to keep homes smelling fresh can set people up for a lifetime of chemically induced illness, and repeated exposure to small amounts of household chemicals can trigger symptoms to previously tolerated chemicals. “The best smell is no smell,” Miller says.”[539.4]

The Lipolytic Gate

We all understand that lipolysis increases following exercise, that different types of exercise are liable to stimulate different degrees of post-exercise lipolysis, and that multiple sessions per day training results in greater lipolysis than one session per day training. Knowing the aforementioned facts, we can begin to look at the lipolytic program as a gate, a gate that is always slightly open, this is basal lipolysis. The more the gate opens, the more fatty acids escape to be utilized as metabolic fuel. When exercise is performed, depending on the variables of blood sugar (glycogen), the gate is opened to a small or great degree, to provide the body with the fuel necessary for the regeneration and growth of damaged muscle tissue. The gate can be progressively opened more and more depending on the amount of exercise sessions performed within a day, but no matter the intensity, duration, or frequency of exercise session, when rest is taken the gate slowly returns to its original closure position over the course of 24 hours, this is homeostasis. Similarly to exercise, specific diets or anti-diets will result in a progressive increase in *Lipolytic Gate opening*.

Unlike optimal and complete myogenesis, especially fast twitch fiber growth, which is best stimulated acutely (one relatively short exercise session in a day for a muscle group followed by refeeding and extended detraining), lipolysis is best stimulated through chronic high frequency processes (two or more extended exercise sessions a day followed by limited refeeding), thus highlighting the dynamics of anabolism versus catabolism. Furthermore, if we understand that detraining, and maximally facilitated myogenesis generally involves the growth of fast twitch fibers, whereas the most optimal training style for the promotion of lipolysis—Endurance Training, when performed at a high frequency, will undoubtedly promote the slow twitch program, then we can connect muscle fiber type to training type and to body composition, which although being quite obvious to any focused observer is important as it reminds us that it is a grievous error to engage in high load training, expecting incorrectly that the severe breakdown and exercise-induced conditioning of fast twitch fibers will accelerate lipolysis to a statistically significant extent (where weight loss is noticeable and easily trackable), which is unfortunately what many personal trainers and fitness gurus will suggest to unfit, and obese clients.

Although altering the Lipolytic Gate is simple in theory, as you can burn fat by simply walking on a treadmill for hours upon hours a day, when foolish diet and health personalities suggest you consume large amounts of “healthy fats” such as high Oleic acid plant oils such as Avocado oil, you will unintentionally increase your IM lipid levels, and over time and with concurrent macronutrient excess, disturb your insulin sensitivity, inevitably making any carefully portioned out “slow digesting” carbohydrates you consume far more adipogenic, and closing the Lipolytic Gate in the process, leading invariably to extremely frustrating and unsatisfying diet results.

Burning fat for a relatively lean individual can take a few months, but for a morbidly obese man or woman who are not dosing anabolic steroids, and overtraining in the gym, burning far more calories, it can take years, which is why you must understand, firstly if you are hormonally impoverished, you can only rely on your willpower and intelligence to reach your physique goals, and secondly that no amount of caffeine or Green Tea extract, or other "fat burners" are a replacement for the ten, fifteen, or twenty hours per week of Endurance Training your body requires to keep the Lipolytic Gate open and experience rapid lipolysis.

Psychological Sublimation, Mental Disorders, & Evil

"Like many other platonic texts (notably *Symposium* and *Phaedrus*), Republic is profoundly concerned with *eros*—that is, "erotic" desire that can find purely spiritual and intellectual as well as physical outlets. Book 9, by no accident, represents the tyrant as overwhelmed and enslaved by sexual desire more than any other appetite, and it thus positions him as polar opposite to the philosopher who, as a "lover of the vision of truth", achieves liberation to the fullest extent."

-Elizabeth Watson Scharffenberger on Plato's Republic.

Forward

My poor teacher Sigmund Freud has been dragged through the proverbial mud ever since death, where even now many colleges currently teach introductory and extremely biased lessons of his most popular work, and label them archaic, illogical, or misogynistic. I sincerely hope at this point in time, you have at the very least taken a glance at Freud's Project to understand how intelligent the man really was, doing so will lend greater believability to what you will read next. For those who hold great disdain (emotionally-based dislike) for Freud without having actually studied his work in depth, please rebuild your relationship with your father as you are clearly psychologically projecting unresolved feelings.

We often forget the impressive psychosomatic connection between the CNS and the brain (mind), so I ask you to consider the mental release you experience after a deep tissue massage, or when you are hugged by a loved one, or when you hold hands with your child, do these phenomenon's not prove the motor pathway as being an important component of the generation or release of feelings and emotions? To act as though we, as Homo Sapiens, have evolved beyond libido is absolutely dangerous, as an animal unaware of its instincts will never overcome its follies.

Part One

Sublimation describes the phenomenon of discharging the libido, or Platonic Eros (Creative energies) through intellectual work, rather than sexual-motor release. Effective Sublimation can always be identified by the hallmark sign of intellectual obsessiveness, or "focus", where the greatest workers are the most skilled at their jobs precisely because work life becomes a replacement for sexual life. Sublimation is not to be confused with "pleasure", because satisfaction only comes at the end of a day of intellectual work or at the end of a completed project, the interim of exhausting neuronal activity is not completely similar to that of sex because pleasure is not continuous but instead delayed, thus explaining why many instinctually prefer to *masturbate* for fast anxiolysis rather than *masticate* (their thoughts) through anxiogenesis.

Sublimation was not discovered by Freud and his earliest psychoanalytic partner Breuer, because during the 1800's sexual frustration was often attributed to female psychoses, and long before that Plato elaborated on it, but nobody has studied the mechanical sciences of the libido more than Freud & Breuer.

In the earliest works of Freud & Breuer we learn that the libido (sum of neurons containing sexual memories) preferentially are discharged by way of motor pathway when the *system*, or the brain, is overloaded, resulting in the development and expression of neuroses, including obsessiveness, and most forms of hysteria. The reason why most individuals do not experience hysteria when they experience sexual deprivation is because their abilities to Sublimate are adequate, often because of increased Environmental Enrichment, exercise, work life, or earlier life psychological conditioning, thus preventing the overloading of their psyches.

If the libido is constantly discharged through sex, intelligence will always suffer, depending on a person's predilection for intellectual work, and this is not only because the brains energies are discharged through a primordial and pathogenic process, but because the more you think about something, the more you are liable to think about that *something*, meaning that behaviors only strengthen in power the more they are reenacted, thus hypersexual individuals become slaves to a very animalistic instinct, and only sexual thoughts fill their head, thoughts which interfere with critical thinking, for not all obsessions are intellectually productive, meaning Sublimation can be unproductive, as displayed by many OCD patients (the ones who Sublimate in unprofitable ways, not intellectually—profitably). We all know that when we study a complicated subject for an extended period of time we become tired or mentally exhausted, even if it is not our bedtime. This is likely because of changes in neurochemical concentrations post-intellectual work leading to reduced brain activity (fatigue), or more precisely, a decrease in *cortical excitation*.

The ability for a human mind to sublimate effectively firstly comes from conditioning and willpower, it is not associated with only healthy or high intelligence. Many cognitively impaired individuals Sublimate effectively at work and at home, but many

more individuals of all cognitive levels are unable to Sublimate effectively. This is because in their ignorance they do not comprehend the majesty of human brainpower and creativity. I believe this ignorance is first taught and developed in schools when children are given bad grades, when they begin to assume they are not *destined* to be intellectuals, to be scientists, to one day reach the stars, and so they are conditioned through scholastic failure to embrace destructive and regressive behaviors.

A human that is unable to Sublimate properly will show signs of intellectual and moral deficiency or derangement. As an example, here is a short case study I undertook to understand a violent crime that was perpetrated by three extremely unintelligent and likely virgin foreign men: In 2018 two young female tourists, Louisa Vesterager Jespersen and Maren Ueland, were kidnapped and beheaded in Morocco by a group of men who found a sick pleasure in [OMITTED] off their heads slowly while they were alive (with rhythm: masturbatory-like), I say they found pleasure in the murders because their murders were recorded and uploaded to the internet, and the knife that used was quite dull. This unforgiveable crime was an animalistic regression and massive displacement of sexual frustrations, they clearly associated beheading with the deflowering of a virgin girl (painful sex) and paid the utmost attention to the process as shown during the low resolution recording of the murders they made, treating the murders like a ritual. There is absolutely no other possible explanation for unattractive young men committing such a heinously torturous crime against two *attractive*, docile, & innocent young women except through the analytical inclusion of the sexual element, for if these girls were kidnapped in a more evolved country, they would have been raped or ransomed, which are the more naturally evolved instincts in 21st century men with deranged libidos. Continuing this line of thought, there is more evidence for a deranged sexual libido being present in terrorists and serial killers, who perform violent acts which ultimately culminate with the *climax* of death, one *explosion*, or one final sigh of their victim. In this regard the violent moral domination evil people seek over innocent people is no different from the domination the archetype (masculine) man exerted on the archetype (submissive) woman during sex, it's the same instinct but it has been twisted and malformed into something new, often technological, and destructive.

Part Two

It is no coincidence that the most classically intelligent individuals on Earth have Been, and continue to be, "nerds" or "geeks" i.e. relatively physically unattractive individuals, ones that do not have easy nor frequent access to sex. They have had to adapt to the exigencies of life through Sublimation, and through this willing expenditure of neuronal energy through intellectual work they have discovered, innovated, created, elaborated, and organized new or old ideas to enrich the world or explain the majesties of life, and sometimes oppositely, to formulate destructive political ideologies, or other high

complexity destructive ideas. Interestingly, the ability to "organize" however simple it may seem, is a sign of functional Sublimation, as it is a form of intellectual work. Jordan Peterson was therefore correct to suggest for you to "clean your room!" before you attempt to change the world, because without Sublimination comes the generation of destructive behaviors and thoughts, although Mr. Peterson unfortunately doesn't understand Freud's earliest theories he still possesses a certain amount of unconscious wisdom.

We all know that *idle hands are the devils plaything*, or more specifically, *idle minds are the devils plaything*. With the advent and spread of pornography we see the destruction of interpersonal relationships, and the creation of perversions that are not only repulsive, but so very strange. Pornography would not be as popular with young men, and increasingly so with young women, if they were taught about the necessity of Sublimation in school at an early age. Instead, children are taught about the act of sex, and pregnancy, but not about the dangers of libido, and this dooms many of them in later life. It is very easy and natural to use masturbation as a release of mental tension when you are a young and healthy man, because the motor pathway is so accessible to the brain (remember the connection between locomotion and consciousness), because men, either because of hormones, genetics, or conditioning, are encouraged and naturally physiologically prefer motor discharge of their libidos, thus explaining why most masculine men exercise more than women, and are more physically, but not passively, aggressive. Women naturally tend to withhold their libidos, which explains the discrepancies in mental illness among females versus men. But because women are not innately predisposed to the motor pathway discharge of cortical excitation, their form of hysteria is often less outwardly violent (person to person violence), and more inward focused—interpersonal (vis-à-vis self-harm). Although the 21st Century woman is now a new creature, sexually liberated, and sometimes equally as sexually regressive and perverse as her male counterpart.

Mental illness is often the lesser of two evils, because if we were to indulge our most simple impulses at all times, especially sexual impulses, a society would devolve into perversions unimaginable. This is one of the reasons why Religion exists, to shape the morality of those who are unable to Sublimate effectively, because most religions contain restrictions on procreation and sex. It was Freud who first posited neuroses as being the negatives of perversion, because he noticed that the most severe forms of neuroses and other mental derangements occurred in patients who experienced childhood sexual trauma. The mental illness and symptoms these traumatized individuals display is the Primary Defense Mechanism of the brain at work, for if the defense fails, hypersexuality and perversion would result, owing to the sheer strength of their earliest sexually-charged childhood memories. Although in his later work he abandoned to a certain extent these revolutionary sexual theories, due to the unpopularity of them, they still exist in his

earliest works with Josef Breuer, Read: The Standard Edition of the Complete Psychological Works of Sigmund Freud: Volume I.

Part Three

In a metapsychological view, the libido was designed to create and to shape life. This can be done either through *sexual procreation* or through *intellectual procreation*. Intellectual work often is a mixture of memorization, extrapolation, and a little bit of creativity, but the most effective forms of Sublimation involve larger amounts of creative expression, this is why art is always associated as both a treatment and expression of mental illness. But I do not believe classical arts will do as much good for society as the scientific arts, such that a man that paints landscapes could have possibly accomplished something more impressive had he taken up the study of architecture or geography, or a woman that enjoys sewing quilts could work towards designing novel fabrics through textile engineering. This does not mean that these forms of creative Sublimation are bad, but it far better to Sublimate in ways that offer monetary gain, or altruistic gain, rather than simplistic creative expression.

Regarding the future of collaborative Sublimation, because comprehensive AI systems such as ChatGPT and Meta AI exist, we are finally able to communicate with a teacher (who is also our student) that possesses vast amounts of knowledge, and through conversation with these AI's we can pursue an autodidactic career or hobby in science without admittance and participation in college. These AI systems, although being similar to human minds, will never reach sentience, and will always be prone to making errors, especially programmed bias, which is actually beneficial, because conversing with them trains our critical thinking abilities, that is if you remember that knowledge and opinion are often convoluted, conflated, confused, or formed through biased sources, and you engage with them in a questioning, or argumentative fashion. The positive encouragement programmed into these Large Language Models is beneficial for a child in learning, but not for an adult, and in their evolving mimicry of human personality will come the further disconnection of man from nature, but this is unavoidable.

Even though I compiled the bulk of this book and wrote the majority of its contents years before I had even heard of a *Large Language Model*, I have found it exhilarating and useful to use them to judge my hypotheses, such as by asking "Is this a logical statement I wrote?: (Insert idea or opinion)", as it is far easier to ask an AI a complex question than a stranger, friend, or family member, who often are too busy thinking and dwelling on the lesser matters of life. AI is a tool that will not cease evolving (to a point), it is therefore illogical to not utilize it to attain knowledge, if you are intelligent enough to question, refine, or correct every programmed response it generates. There is no doubt that these new tools of knowledge will be misused by individuals who begin to treat them as conscious entities and not simply as convenient depositories of information, those who

will replace a pets affection for the feigned affection of a new pet, one formed with transistors and vastly complex coding.

Though it be true that all Large Language Models will datamine your inputs, you are capable of doing the same, especially if you ask these AI's complex and useful analytical questions, as you will then be learning from them to the same extent as they from you, which although being an unnatural dichotomy, will be a necessary choice in response to the acceleration of human vapidity and pronounced lack of inquisitive thought among young people who continue to embrace the path of sexual and emotional regression facilitated by bad parenting, and chronic recreational drug abuse. I must clarify that just because LLM's are growing in intelligence, this does not mean you should rely on them for doing research for you as you cannot program human ingenuity into digital code, and considering firstly how easy it is to search for extremely precise PubMed articles simply by changing your wording while on Google, or Bing, and secondly that if you never learn how to research, correlate, and contrast actual complex medical literature through your own volition, and simply rely on simplistic Healthline articles, you will be at an intellectual disadvantage.

Returning to Sublimation, a complexity regarding it in my opinion is that it can be split into two types; *Naïve Sublimation* and *Intellectual Sublimation*, the former is a hallmark symptom of overthinking mundane topics, or any purely mental or motor obsessive-repetitive behavior, whereas the latter involves expending cortical excitation on more complex cognitive problems, most of which improve human existence, such as the study of a science. Such that if you read a book, you're clearly engaging in Intellectual Sublimation, but if you obsess over a love object (an ex-girlfriend or boyfriend) or if you obsess over relatively uncontrollable subjects in life that involve simplistic emotional patterns of thinking, you're engaging in Naïve Sublimation. Naïve Sublimation is the primary natural process in the brain, most people do not actively seek out cognitive challenges, they seek comfort in psychological homeostasis, where new emergent phenomena & stimuli are avoided in waking thought. It requires willing effort (or forced deterministic conditioning) to learn new things and think creatively with an analytic bent. There is clearly a difference in Sublimation between Salvador Dali's complex art and Mark Rothfields' simplistic art, which is not to say there are not admixtures of these types of Sublimation processes, or that Naïve Sublimation can produce no beauty or intellectual products, but it is healthier for the analytical intelligence of a human being to engage in Intellectual Sublimation, even if it requires greater effort, time, and ERN.

Exercise is surely the most natural and beneficial form of Naïve Sublimation, considering it increases intelligence, which is why in a perfect society, those with the lowest intelligences would exercise the most, and when I say exercise I refer to cardiovascular exercise, not strength training. Unfortunately, the unhealthiest and most dysfunctional minds often only exacerbate their cognitive decline through living sedentary lifestyles, or obsess over and only engage in higher load resistance training,

that of which only benefits their minds to a small extent, and results in injury development. We all understand that any form of exercise will benefit a dysfunctional brain, but we forget that the most sustainable forms of high intensity training are Cardiovascular-based—the classical cardiovascular exercises involving microrepetitions, such as walking, jogging, running, cycling, boxing, swimming, et cetera. Beyond neurogenesis and brain lactic acid saturation, leaving aside the less common forms of safer high load training such as those involving Isometrics, or Partial ROM exercises, Cardio will always be the greatest and safest way to discharge by way of the motor pathway excess cortical excitation.

I must clarify that following the same line of Freudian thinking, I believe Naïve Sublimation is an essential component of a happy and balanced human life, and that a person can only engage in Intellectual Sublimation for so long before they need a "motor release", which is why both women (access to sexual satisfaction) and exercise play the role of an anxiolytic for most men, leaving aside hypersexuality, and this is applicable for women too. If a man or woman neither exercises, nor has access to sexual satisfaction, they may possess a high intelligence, but they will suffer from a high baseline level of anxiety, and possibly other neuroses, and this effect is magnified in women who are unable to discharge their libidos as easily as men. For any mathematical system conscious of its processes (our brain) to exist within a state of high energy would be predicted to "feel uncomfortable" as it most often does, but anxiety is the price we pay for intellectuality and intelligence, hence the reason why we consume caffeine upon waking, to stimulate us into action, to increase the energetic power of the system, but how we utilize our neuronal energy, our excitation, leads us to a complicated metaphysical and moral quandary.

For many the answer to sexual frustration, the inability to properly Sublimate, the treatment for many forms of hysteria and neuroses, is quite obviously, sexual liberality. But as most intelligent minds have learned, the Sexual Revolution did not benefit mankind, and when it blended with technology, it's poison only grew in strength. The supremely evolved Sublimation abilities of the greatest thinkers who have graced our Earth is the exact reason for their intellectuality—their inventions, and their discoveries. The fastest way to nullify a society intellectually is to promote, and to condone hypersexuality, to condition the citizens within it to discharge their cortical excitation impulsively, animalistically. This is the primary folly of the newly irreligious Western World, to attempt to spread its perversions overseas to the societies that have not yet experienced the intoxicating and corrupting luxuries of excessive consumerism, overconsumption, and unrepressed sexual freedom. There is no doubt that even impoverished nations have been corrupted by the unlimited access to the internet, where the libido is allowed to roam free, and regress to its simplest method of release, but there are still bastions of morality in the world, where a child has parents who teach them right and wrong, instead of ignoring them, and allowing them to be raised by hyperemotional,

hypersexual, and vapid social media, such as through Snapchat, & TikTok, where no intellectuality can be found.

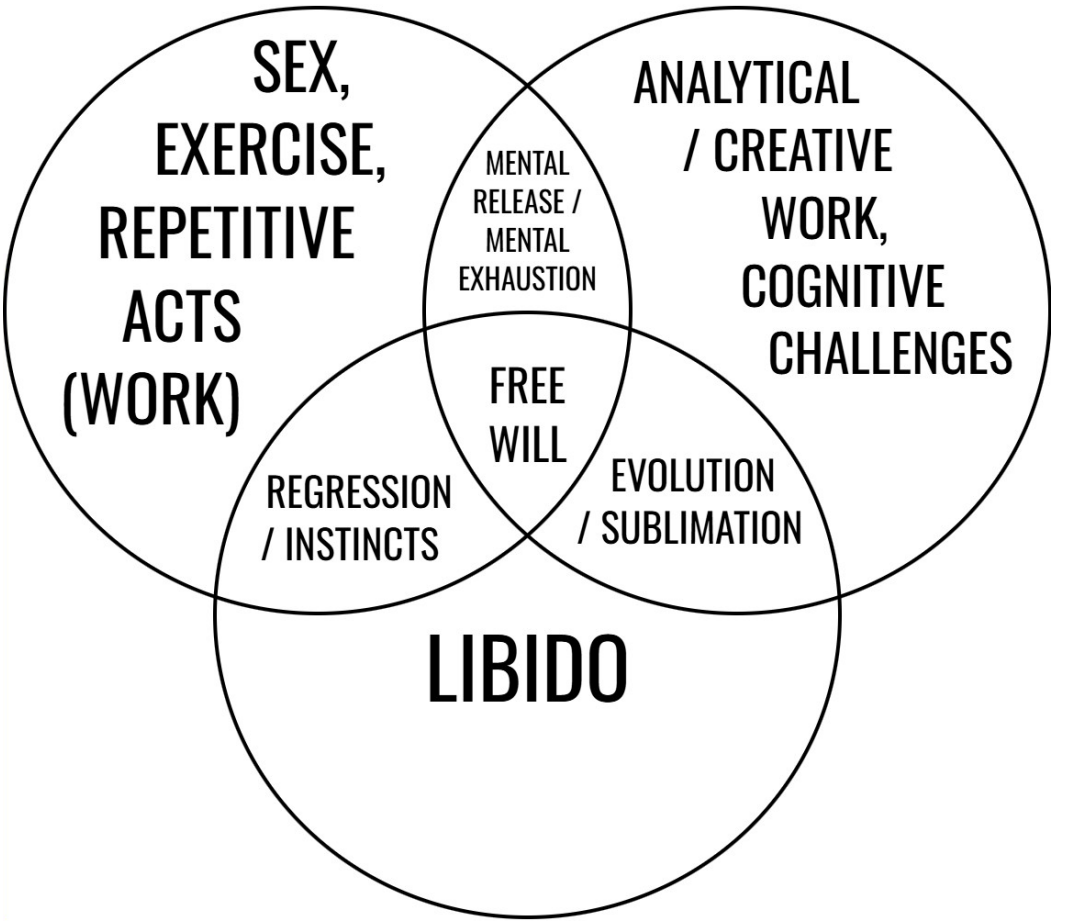
Returning the libido, even a model organism, which is an organism with similar genetic similarity to us, and therefore used in research studies, Drosophila Melanogaster, or the common fruit fly, experiences psychological (neurological) consequences of sexual deprivation and displays signs of sexual frustration-induced drug seeking behavior (exactly like human drug use patterns):

"<>The brain's reward systems reinforce behaviors required for species survival, including sex, food consumption, and social interaction. Drugs of abuse co-opt these neural pathways, which can lead to addiction. Here, we used Drosophila melanogaster to investigate the relationship between natural and drug rewards. In males, mating increased, whereas sexual deprivation reduced, neuropeptide F (NPF) levels. Activation or inhibition of the NPF system in turn reduced or enhanced ethanol preference. These results thus link sexual experience, NPF system activity, and ethanol consumption. Artificial activation of NPF neurons was in itself rewarding and precluded the ability of ethanol to act as a reward. We propose that activity of the NPF-NPF receptor axis represents the state of the fly reward system and modifies behavior accordingly."[539.4.1]

To aid in comprehension, I have formulated a simplistic cascading explanation and reference guide of Freud & Breuer's mechanical psychology, and created a Ven Diagram and on the following page.

- the libido = excitatory / excitation-producing neurons (libido neurons)
    - libido neurons = increased firing of action potentials
        - sex = exhaustion of cortical excitation produced by libido neurons
            - reduced cortical excitation = reduced synaptic plasticity = decreased intelligence

- sexual deprivation + sex hormones + sensory priming + excitatory tone = accumulating cortical excitation
    - excess cortical excitation = neuroses / psychoses
        - anxiety / obsessiveness = increased cortical excitation
            - hysteria = rapidly discharged cortical excitation through the motor pathway
                - sublimation (intellectual work, exercise) = the displaced utilization of cortical excitation
                    - efficient sublimation = the generation and maintenance of complex intelligence



If you do not believe in Free Will, although you may consider the following Diagram to be inefficient, you may replace “Free Will” with “Psychological Conditioning” as either way it does not change the impressive value of comprehending how the human libido operates.

To clarify my stance on the libido, I do not believe all mental disorders are the result of libido derangement as there are many more variables that play a role in our mood and our memory, but whether it be environmental toxins, or recreational drug abuse, the greater neurotoxic processes ongoing in the brain, the more difficult it is to Sublimate, which will often lead to intellectual inferiority, criminality, and self-destruction. One must remember that our instincts reign supreme, and sexual libido facilitates urges or needs that for most are far stronger than hunger, thirst, or tiredness. And as a preemptive retort to those who consider this all to be pseudoscience, you are free to exist in the darkness of ignorance, where you do not see the continuance of patterns of ancient cellular life, where the processes of viral horizontal gene transfer and mitosis reemerged in the form of a novel and beautiful life process called meiosis, where the human libido was formed, only to be

reshaped and redirected through the forced need for sociality, to enhance survivalism, eventually leading to the formation of, and destruction of every single civilization.

For more information on Freud's earliest and most obscure sexual-mechanical theories on the libido, read The Complete Psychological Works of Sigmund Freud: Volume I-II. If you instead choose to learn from Freud by proxy, from the words of his detractors, and from condensed college courses, you will never truly understand his work.

Consciousness Continued

It is my hypothesis that consciousness developed from not only endosymbiosis and the formation of mitochondria, but also *microbial diversity in the digestive system*, and this is plausible considering that both beneficial and *pathological* bacterial organisms that live within our intestines are capable of producing extracellular vesicles, many of which alter our neurological function, our moods, and our memory.

Even spiders and bumble bees have a microbiome that is present and alive in their digestive system, and I can't help but think this is more than a mere coincidence. For this would explain the depersonalization and neurotoxicity that develops when we take broad spectrum antibiotics. Is it not possible that our bodies and even our brains are influenced by something even more primordial than inherited memories stored within our unconsciousness, by the bacteria that evolved and mutated long before we did, the subspecies of organisms that have existed on Earth and possibly far beyond Earth for billions of years.

I believe it to be possible to strengthen a society or weaken it through promoting the growth of certain strains of gut bacteria either through bad prebiotics (i.e. processed foods), good prebiotics, or the consumption of certain fermented foods. Although I would never suggest that a person's microbiome is *entirely* associated with their emotional intelligence, as that involves conditioning above all else, it is an irrefutable fact that an unhealthy gut invariably leads to an unhealthy and weak mind. We should study what the microbiome signature of certain geographic peoples means for metrics beyond classical intelligence, such as the emotional patterns anger, fear, anxiety, happiness, and more complex patterns of thought such as humor, lust, & depression.

It may be possible that I am overcomplicating this idea, that neurotransmitter levels have led to the generation or continued evolution of consciousness, but then we must remember that many microorganism extracellular vesicles carry neurotransmitters as their "cargo" to fertilize the brain, *to power it*. Regardless, it is an interesting thought to ponder, are we simply electrical activity and nerves, or is the brain a machine that operates to protect and house our true masters—our forgotten ancestors?

Purposeful Exercise Asymmetry

We understand that exercise machines that are not leveled or fabricated incorrectly are capable of creating instabilities in our muscles and motor patterns, thus resulting in eventual injury. But what about planned or programmed exercise Asymmetry? Bill Kazmaier said in a seminar that he would deadlift one inch off of center to the left or right, to develop a stronger back[539.5]. And this is logical, for after a quick search of Franco Columbu posing, we are able to notice larger lat development on his right side than left, due to his mixed grip-use during powerlifting deadlifts. I suggest therefore to experiment, infrequently with this form of training by adding one of two asymmetry variations during a workout with low-moderate loads at first, and eventually moderate-high loads if you are able to master the novel motor memories required.

Even if this old but novel form of training does not improve your strength, or result in accelerated hypertrophy, it will surely build your core and antagonist muscles, making it a very interesting and beneficial addition for powerlifters who rely heavily on these muscles to maintain optimal form during near-maximal force exertion. Also, there is something very fun about changing how you train, learning new motor patterns, and challenging our minds.

Asymmetry Variations:

Kazmaier “Offsets” A: Start barbell movement an inch to the left or right of center, lift barbell while maintaining perfect form and core stability (abdominal tension) throughout ROM, alternate asymmetry each set.

Kazmaier “Offsets” B: Unload one side of barbell by 5%-100%, lift barbell while maintaining perfect form and core stability (abdominal tension) throughout ROM, alternate asymmetry each set.

The Necessity of Upper Body Cardio

Cardiovascular exercise involving the leg muscles is clearly the most important type of cardiovascular exercise, as it is capable of eliciting the greatest changes to heart rate, and the leg muscles are more resilient to damage and overtraining as compared to the arms and shoulders. But this does not discount the necessity of Upper Body Cardio, as it is important to train large muscle groups similarly, to achieve balance.

Generally speaking, the muscles that are the most resistant to aging-induced atrophy or weakness are the legs, and this is because they are most often trained with high repetition—with microrepetitions—during cardiovascular exercise or during daily

locomotive necessity, giving the leg muscles denser mitochondrion, greater glycogen storage, and a far superior blood vessel number. This discrepancy in training type, frequency, and volume will eventually present its deleterious effects in later life.

If you have a high income you should buy a handcycle, or a Sci-Fit machine, or find a gym with one of these training tools, because they incorporate the most upper body muscles intra-workout and are ideal for upper body *steady-state cardio*. Even if you prefer to specialize and strength train an upper body muscle group, it will only benefit your chosen muscles to deload with high volume microrepetition exercise, that of which is highly angiogenic. For those without the aforementioned upper body cardio options, there are 1" (light weight) x 40ft long Battle Ropes, seated rope pulling apparatuses, or resistance band rowing, where you can sit on a rowing machine, attach a resistance band with handles to the monitor area, slide to the rearrest portion of the rail, and row without the legs involved, but remember you should never use traditional rowing machines as they will only overtrain the distal area of your biceps brachii due to the strange spread of tension and torque of the movement. Finally, you could experiment with what I refer to as "Standing-in-place Boxing" where you throw rhythmic punches to maintain a heart rate, without moving the legs or lats.

Autodidactism

As I have mentioned before, this book has only been made possible by the countless hours and meticulous work of researchers who have done far more for the evolution of science than I have or will ever be able to. Because I respect their research, I have copied, pasted, and organized their collective words, thoughtsd, and meanings without purposeful obfuscation.

The goal of this work is to not only enlighten the average reader, but to stimulate within them an interest in research, of creative correlation, of "PubMed Journey's", as I call them. Self-sufficiency has always been important for an organisms survival, and although it may be easy to listen to one voice, one internet personality, for your biomedical knowledge, it is foolish not to become at the very least semi-efficient at understanding the sciences of your body and brain.

Researching the pharmacodynamics of prescription drugs is very interesting, and not too complicated, and every inquisitive mind should begin their foray into biomedical research through that field, before the others. What should invariably follow is research into the chemical composition, pharmacodynamics, and pharmacokinetics of phytochemicals, and then a progression into any other applied human science.

PubMed is currently open to the public, but this will likely not be the case forever, as politics change, and a more dystopian future comes into play. Therefore, it is vital that one makes good use of the over twenty-seven million articles on PubMed to their

advantage before this massive and ever-growing library of science is lost forever or locked away.

If you feel too inferior mentally to research in your own time, you must ask yourself this question; “Do I fear knowledge?”. We are conditioned genetically to put our faith into in the hands of men and women who wear white, and although many doctors have good hearts, many more have bad hearts, narcissistic personalities, and very low intelligences, hence medical malpractice lawsuits, and the extreme commonality of incorrect diagnoses, apathy, and gaslighting that patients must experience when seeking competent and caring medical care. If your doctor is offended or illogically dismissive when you ask detailed and informed questions about your health or a certain drug or therapeutic treatment option, or if you bring your own research up in conversation with them, they are not fit to practice medicine, and you should use this as Litmus Test to discern who is worthy of your medical respect, and who is not.

In all my years on Earth, I have noticed that the majority of our elderly persons seem to put near absolute faith into their doctors and the medical field as a whole, and yet many of them are poisoned in the end stages of life by the unnecessary use of prescription drugs, and although it is in our nature to seek out guidance and solace from people who claim to have a connection to Heaven, or those who claim to have an intimate connection to intricate sciences, it is dangerous to ask life changing questions and receive answers in a language that you do not understand. The language of science must therefore be understood better before you even attempt to have a conversation with a doctor, if you wish to make the most logical decisions, to decide what drugs you actually require, or what therapies may benefit you. It is far better to be skeptical, and ask obvious or dumb medical questions than to blindly follow any advice a specialist gives you, for you may better comprehend your physiological state, or you may better understand the sciences you have been forced to embrace a study in through the unforeseen development of a sickness.

Testosterone Replacement Therapy

It is true that I hold great distaste for anabolic steroid users who belittle natural lifters or normal gymgoers, and more importantly I despise enhanced athletes that offer or are paid to create training programs for natural athletes that invariably leads to overtraining or injury, but I am not against testosterone replacement therapy, nor am I against anabolic steroids, I am against the false equivalency of training and recovery.
Testosterone and Estrogen are essential hormonal components that delay cellular, or at the very least, brain aging, and their replacement during the natural course of human aging should not be ignored in the 21st Century.

A total testosterone level of less than 300 is generally considered to be “low”, but in men I believe any total testosterone level below 700 is deleterious to our confidence, muscle recovery, sleep, and memory. Finding a TRT clinic that will give you a fair dosage of testosterone cypionate is nearly impossible locally, but possible through the web, where you should strive to get approved for a dosage of 200-400mg per week. Most importantly, it makes absolutely zero sense to be prescribed intra-muscular testosterone cypionate once every two weeks, considering its half-life is 4.5 days, mood swings will invariably occur during the end of the first week during the later stages of withdrawal, paralleling muscle weakness, therefore, always ensure your TRT is on a weekly basely, unless you’re using pellets or longer acting forms of testosterone.

Although I believe relying on the pharmaceutical industry for gaining mental or physical strength is similar to playing with fire, when it comes to hormones, because they are such beneficially potent physiologically active substances, there is no other choice than to embrace HRT, that is unless you find yourself on acres of silent land, far beyond the emotional, chemical, & noise pollution of big cities, wherein you can age gracefully, and truly naturally.

The Medical Rubicon

I have visited a few assisted living homes in my time, and I always took notice to the fact that these abandoned elderly individuals who are confined within these “homes” or “facilities” are provided inferior diets, extremely low in protein, high in fast digesting carbohydrates, and devoid of phytochemicals. Furthermore, and quite obviously, all of these elderly, and often sickly individuals are deficient in hormones, hormones that could reverse their neurological and physical decline. Why do assisted living homes not mandate hormone replacement therapy for the elderly? We all inherently know the benefits of exercise; we all know that exercise is capable of protecting the brain from degeneration, but how do you expect a frail man or woman to exercise intensely when they can barely walk without assistance due to severe muscle atrophy? And what about diet; how is an elderly man or woman with dementia supposed to recover from his or her neurodegenerative condition when they are fed simple sugars and saturated fats that only accelerate the molecular trash being deposited into their brains?

Leaving aside the paralyzed, as a thought experiment, what would happen if sickly patients in assisted living homes were to be fed high protein-high essential fat diets, and administered testosterone or growth hormone replacement therapy, and exercised effectively through safe but intense strength and cardio training protocols and not random exercises designed by personal trainers with pea-sized brains. Would most assisted living homes not be empty if they actually rehabilitated individuals?

In all honestly, it is not the job of an assisted living home to take care of your aging mother or father, it is your responsibility. And if you learn how to eat properly, and how to exercise effectively, reversing or delaying the physical and mental aging processes that

your parents are experiencing is extremely possible, if at times highly irritating, if you're willing to invest the time in teaching them how to train and eat intelligently. In scenarios where you have no free time to care for your sick parents, there is still ample opportunity to visit them, exercise them, and feed them properly, to at the very least provide them with enough physical and mental strength to face death with vitality and dignity.

The idea of a *Medical Rubicon* is a term I coin to mean "a medical condition that is said to be untreatable, or uncurable", it is a myth perpetuated by intellectually lazy physicians, and a byproduct of pathetic rationalization on the part of family members—for to say "this cancer is beyond treatment", or "her Alzheimer's is too far gone" is an easy excuse not to experiment with extremely high dosages of phytochemicals, intensive exercise protocols, severe dietary changes, VOC's, or many other forms of alternative medicine. And if alternative medicine fails, then you can say that you, and potentially and your loved too, did not give up, that you both fought death to the bitter end.

A society that puts its faith into medical institutions is bound to embrace the "final stage" or "terminal" futility thought pattern of fighting against death i.e. embracing the processes of cellular decay, of entropy. To believe a medical condition is beyond treatment is to embrace medically assisted *intellectual* and eventual *actual* suicide.

Regarding medically assisted suicide, it is strange that the chronically depressed and chronically ill often treat themselves as *cancerous cells*, and contemplate or choose to commit *apoptosis*, while the true cancerous cells of society, the pedophiles, rapists, murderers, and psychopaths fight voraciously for their right to live.

Those who are severely ill, either by way of mind or body, but morally innocent, often have a purpose that can only be achieved through attrition, and they must be informed they are capable of reversing their chronic health conditions through the correct application of complex knowledge. A knowledge that their doctors will likely not hold, and that they, or their loved ones (you) will need to acquire by embracing and forming an obsession in applied human sciences research such as phytochemistry, pharmacodynamics, pharmacokinetics, neurology, and physiology. A society that is self-sufficient is one that is free from the tyranny of outward incompetence.

In the not-too-distant-future, many people, especially ones suffering from depression, will be fooled by doctors into thinking that how they feel at their worst is how they will feel forever. And in believing that grievous lie they will find solace in embracing death, either through assisted suicide, or other severe medical interventions, instead of gathering and utilizing the tools necessary to wage war against entropy—those being essential nutrients & phytochemicals, and combining them with the most primordial therapy for neurological adaption, which is higher intensity forms of cardiovascular exercise.

Accumulative Muscle Damage vs Overt Overtraining

Muscles are capable of adapting through mechanotransduction to almost any exercise, but there is an important distinction to be made between accumulative muscle damage and overtraining. The former is an inevitability of high frequency training, and the latter is an inevitability of causing too much muscle damage during a workout, as high frequency undertraining will most often be more anabolic than low frequency overtraining. There is of course nuance in the aforementioned statement, for if you train a muscle group everyday with moderate loads, but the volume is high, you may grow less muscle than if you train a muscle group once a week with very high loads, but very low volume.

If you are not a powerlifter or professional athlete, it would be much wiser to train for accumulative muscle damage, by avoiding high loads for the majority of your workouts, to ensure that when injuries present themselves they are minute and easily rehabilitated. This can be accomplished by training with steady weight, rather than constantly trying to break your 1RM with overload training, which is not a sustainable form of training.

The greater muscle damage that occurs in a workout, the greater number of stem cells are required to repair those muscles for both the early and late stages of myogenesis. If therefore you choose to always train with high loads, high volume, and high frequency, you will experience injury, or a myogenic plateau at some point, unless you are able to substantially magnify stem cell proliferation post-workout such as through the use of various supplements, modalities, or drugs. Therefore, for the majority of the readers of this book, who are natural, it is a better idea to never train to failure with high loads, and always keep your higher load resistance training low volume, such as only choosing one or two exercises per exercise session for your *working sets* (high load sets) and keeping the total Load Volume reasonable. You must plan for the distant myogenic future, not for the immediate myogenic future, that is if you wish to continue to progress through resistance training.

Even if you train a muscle only twice a week with low loads, accumulative muscle damage will still occur, making it necessary to deload with even lighter weights at certain points in time, detrain, or change exercises, that is unless you have access to either anabolic steroids or one or more myogenic modalities to accelerate wound healing.

It is not always foolish to engage in high load resistance training twice a week, if the range of motion is reduced, which is a common argument geared powerlifters make when they say *less ROM = less risk of injury*. Utilizing bench aids such as boards (board press), a Slingshot, or Titan RAM during your bench press workouts is not cheating, it could be a way to avoid injuring yourself on a high frequency-high load training protocol, if you are unwilling to deload or detrain, or approaching a competition. Regardless, in the end the most intelligent way to train is to train carefully, to not get “high” every workout on caffeine and train like a madman. To prove my point, research any geared bench presser that trains with more than 1000lb’s pounds, and you’ll see the longevity that reduced ROM lifting affords.

It is logical to suggest that if you are a novice lifter you set long term goals that those around you would consider too easy or require too long of an amount of time attain, because these goals are realistic, and although underwhelming they are highly achievable. Remember, recovery from a workout is more important than the workout itself, for exercise recovery is not only muscle repair, but cellular adaptation, and cellular adaptation will only occur when the body is capable of adapting to the magnitude of stress (load *x* volume *x* tempo) you put it under. Before each workout you must deduce what the benefits of success and what the detriments of failure are, if you have a sore shoulder and still choose to overhead press high loads, are you not simply slave to the peer pressure of your friends or the unconscious peer pressure that is generated within you when exercising in the presence of youthful athletes, or from the memory traces of viewing enhanced athletes training, who are indirectly influencing your decision to risk injury?

In terms of overt muscle damage that occurs during extreme tempo training, especially superslow training, even if you provide your muscles adequately long detraining times to regenerate, this will never be a sustainable way to train without the inclusion of ARCS to maintain optimal systemic cellular health, and unless your ultimate goal is to continually increase your top-end strength, for the majority of people, general health comes before top level muscular function, and its far better for the muscles, brain, and heart to cycle between training types and techniques.

Plant and Fungi Metapsychology

Part One

Plants do not possess consciousness, as they display only reactive behaviors and not proactive behaviors (forethought), but it is still puzzling why they form the bulk of our diets, if many phytochemicals are in fact exogenous pesticides produced by the plants to dissuade or to poison herbivores, which are their primary predators.

While it may be true that many of the plants and fungi we consume in our diets are not species that possess high concentrations of phytochemicals and mycochemicals, why is it that for millennia herbalism has existed, and from herbalism has come pharmaceuticals. You can't just label that as a coincidence, and suggest it be a consequence of the improbable good luck of chaotic emergent phenomena. Either plants do possess consciousness and produce phytochemicals for multiple reasons, one of which is to treat our ailments in the *hopes* their species continue to be cultivated (reproduce), or plants are non-conscious entities that were genetically programmed, likely through viral infection similar to us, to produce phytochemicals as both a defense against herbivory, primarily insect herbivory, and to promote health in human beings. Darwinism, as discussed before, does not explain viral horizontal gene transfer and drastic changes to a species form and

function during evolution, you therefore cannot suggest that we shaped the evolution of plants, such as through domestication, as many species are still highly poisonous.

Now one may ask, why are some plants poisonous while others are relatively safe if they were *designed* through concurrent or targeted evolutionary viral infection to be used for nutrition (vitamins, minerals) to further our evolution, and as health remedies? Well, quite clearly to me, the most poisonous phytochemicals exert the most potent anticancer effects. The topical use of these compounds may be beneficial for repressing tumors or skin cancers, even infections, and the extraction and isolation of these compounds and targeted delivery to diseased tissues is a very promising idea. We must also remember that many major pharmaceutical advancements in medicine have come from the study or extraction of phytochemicals, from the antibiotic Penicillin that is naturally produced by the mold Penicillium notatum, to the antimalarial chemical Quinine extracted from Cinchona tree bark, to Salicylic acid (Aspirin) being extracted from the Willow tree bark.
It is obvious that the greatest pharmacy in existence exists in the wilderness, where the most potent medicines grow and flourish naturally, untainted by science and technology.
It's true that even the most beneficial phytochemicals often restrict growth of healthy tissue or reduce reproductive fitness in humans, but these are side effects that are necessary for the quelling of inflammation and protection of DNA.

If one is to argue with the status quo that we use toxic plant and fungi chemicals—many of which are exogenously-produced pesticides—in our environment out of necessity alone, and through human adaptation and microdosing we avoid noticeable toxicity, that would suggest that our cells were programmed to adapt to extremely specific environmental toxicants, which only ties us back to the original point. This theory of random complexity also does not explain the statistically improbable odds of having such a wide array of worldwide and often locally grown plants and fungi that *naturally* contain extremely powerful anticancer, antiviral, and antiparasitic chemicals within them. The majority of safe-to-consume plants and fungi are clearly here to help us, and the unsafe-to-consume or *highly toxic* varieties hold hidden potential for treating the most devasting biological diseases. We must agree with the ancient wisdom that taught plant medicine as being a blessing that originated from the gods, the gods who resided in the sky, the heavens, that being space (panspermia).

Part Two

It is amazing that before we had doctors, we had shamans, monks, sages, hakeems, and ayurvedic practitioners who used herbalism to treat a wide variety of ailments, and though it is dangerous and difficult to use herbalism effectively without accurate identification and quantification (chemical profiles) of herbs, it is still quite impressive that men and women of old were creative enough to form medicines from nature.

Ironically, even with the general increase in human intelligence that has accompanied technological evolution and lead us to where we are today, many medical professionals are no more intelligent or wise than the most ancient herbalists.
Not much has changed over time, as the common psychiatrist or doctor is able to name dozens of psychotropics but cannot explain the pharmacology of said drugs, while so too the ancient herbalist would have been able to name dozens of medicinal herbs and their indications but would know nothing of their chemical compositions or the actual pharmacology, only having empirical views of their pharmacodynamics.

Both old and new practitioners of medicine operate through large amounts of intuition and critical thinking (Empirical knowledge) but owing to a lack of study and comprehension in pharmacodynamics, pharmacokinetics, physiology, and neurology, the logical fallacy of Post Hoc Ergo Propter Hoc is liable to occur frequently. What separates ancient herbalists from 21st Century medical professionals is that ancient plant medicine was based solely on both practical knowledge and mythology because of a lack of scientific tools and knowledge available, but today there is no excuse for a doctor to prescribe a drug that has a mechanism of action that is anathema to them.

In closing, I will remind you that we now live in a society where knowledge is freely accessible, thus allowing us to become highly informed patients, and although many of us already believe we are treating our health prophylactically by taking popular antioxidants, or vitamins, we do so often in willing ignorance. It is important to use critical thinking abilities and to develop a habit in researching pharmacology to prevent oneself from being manipulated by both supplement and drug company advertising and internally generated Placebo effects.

To *Slow* cellular aging

It is my opinion that although it is true that we lose our fast twitch fibers as we age, either through transition processes or apoptosis, it should still be the goal of any older man or woman to embrace the slow twitch phenotype through Endurance Training.
This is not simply to stay lean through enhanced metabolism, and look good, but because every important cell in our bodies runs on mitochondria, most especially our delicate brains, which were not designed to only think, and wonder about the world, but to be strengthened through exercise—the most primordial nootropic. The greater number of slow twitch fibers you have, and the greater their mitochondrial densities, the greater physical endurance you will have, which will equate to longer workout sessions, leading to greater blood flow to the brain, greater lactic acid saturation, and delayed systemic cellular aging.

The body was made to move through repetition, and it is only through innumerable repetitions that the brain begins to function at higher levels. Although high intensity cardiovascular training has the benefit of promoting neurogenesis in the brain, the fact that it causes immunodepression proves that high intensity training is not something the

body should be exposed to at a high frequency, for we adapt slowly to extreme external pressures. To strengthen your slow twitch fibers through aerobics and endurance training is to embrace the movements of your ancestors, who traveled across the world, or across their own land masses by foot to forage and hunt for food.

The necessity of having fast twitch fibers is directly proportional to carbohydrate consumption, as insulin resistance and accelerated aging will occur in individuals who lack fast twitch fibers on high carbohydrate diets, but as we have learned, to suppress the insulin pathway is to enhance lifespan in many scenarios, therefore if you are determined to extend your lifespan while not engaging in high frequency Endurance Training, *you must restrict your dietary carbohydrates*, which will undoubtedly decrease your abundance of fast twitch fibers, especially over time, as energy restriction leads to the facilitation of a slow muscle phenotype. Therefore, to engage in high volume endurance exercise at a young age and condition your slow fibers (especially if you are a natural athletes) will undoubtedly delay at the very least muscular aging, considering fast twitch fibers naturally weaken over time, you will be able to adapt early and efficiently to skeletal muscle fiber-type aging.

I am of course not saying strength training is useless, as fast twitch fibers are beneficial towards maintaining stable blood glucose levels and facilitating high intensity cardiovascular training, and the tendons will only grow when subjected to higher loads, and finally bone density will only increase through high load training. But I am making the argument that mild endurance training (60-120 minutes at or near 65-75% max heart rate) is the best way to slow systemic cellular aging, and therefore should be performed all throughout life, even if you need to scale back or delay your strength or power goals.

Animal Testing Ethics & Bioweapons

It is clearly morally wrong to house animals in uncomfortably small cages and subject them to the tortures of drug or surgical experimentation. I do believe there would be enough human volunteers for incorporation in studies to continue to progress in our understanding of phytochemicals and research chemicals. Regardless of the future legality of animal testing, the animal-based studies we have now should not be discarded for the sake of moral high ground.

If twenty thousand mice, kittens, or dogs were the required scientific sacrifice to save one child from perishing due to a genetic condition, I would not hesitate in making that choice, not because I don't care about animal suffering, but because I consider the life of a child to hold a value that is far greater. Unfortunately, because we are ourselves animals, we are prone to making grievous logic errors, and with them come the unnecessary suffering and deaths of lab rats due to flawed study designs, or worse, *redundant* studies. Therefore, continuing to entrust all scientific innovation of human health and wellness to only doctors, researchers, and government officials is unwise and

extremely dangerous. Self-experimentation of drugs and modalities is an intelligent expression of freedom and is ethically sound and should be encouraged by medical professionals.

As a clarification, I do not mean to suggest that scientific researchers are bad actors in human health affairs, but they live in an echo chamber, and we must learn to eavesdrop, and decipher their strange scientific language, or we fall prey to the downstream over-simplified & antiquated medical treatment recommendations given to us by doctors who don't even subscribe to even *one* scientific periodical, leading to a continuation of the microcosmic "Dark Age" of the medical community, where many patients know more about pharmacodynamics and research chemicals than medical professionals.

Animal testing is a double-edged sword, it has clearly saved an amazing number of human lives, but it has also eroded the morality of certain men and women who consider themselves gods, and therefore capable of saving the human species from its own animalistic folly. It is not unreasonable to suggest that certain laboratories are actively developing bioweapons, likely ones with antifertility actions[1]-[2], for use on the general public to quell "overpopulation". This is plausible considering that many scientists, although rich in intellectual spirit, are devoid of emotional intelligence, and consider the future of our species survival as being more important than individual human freedoms and autonomy, such as the freedom to procreate. A scientist may live forever through his or her published intellectual works, but for the majority of non-experts, procreation and child rearing is the only lasting mark they can leave on society, and to deprive them of this is a crime against the very first cell that proliferated through mitosis on ancient Earth, *or beyond*, and it is a species-wide death wish that should not be tolerated.

[1] "<>This article discusses the possibility of adding antifertility substances in staple foods or in water supplies to help control the world's population explosion. Similar antifertility experiments done on dogs represent the first, organized, large scale proposal for controlling a population in such a manner, and may have important implications for humans. Projections of the world birth rate reaching 7 to 14 billion in the next 2 decades may be cut in half if zero population growth were accomplished. However, due to prevailing ignorance and restrictive traditions that dominate today's global realities, birth control planning is hard to enforce. Although much easier to institute in affluent societies than in less developed countries, mandatory birth restrictions pose many ethical and legal problems. Population control involves several approaches or a combination of all: 1) education, 2) chemical additives and, 3) physical obstruction. The primary birth control method of chemical infertility by voluntary or compulsory methods, could be programmed temporarily, permanently, or according to sex. Although problems such as: 1) the ability to regain a fertile state if desired; 2) possible genetic changes in future generations; and 3) carcinogenetic and severe psychological effects are major concerns,

applying these methods may be justifiable when millions would otherwise die of starvation."[539.5.1]

[2] "<>The principle of animal population control through the use of sexually sterile males has been demonstrated for insects. Sexually sterile males that retain their sexual vigor and behavior will exert greater influence in regulating animal populations than can be achieved by destroying or removing the same number of individuals from the population. This hypothesis is supported by calculations showing theoretical population trends in assumed insect and animal populations subjected to treatments that destroy or eliminate certain percentages of the individuals as compared with a procedure that retains or replaces the same number of males in the population after sterilization. The maximum regulating effect that can be achieved is in direct proportion to the ratio of sterile to fertile males competing for mates. The advantages of inducing sexual sterility in a natural population of an insect species by chemical or other treatment over the method of rearing and releasing a dominating population of sterile males are considered. It is suggested that the sterile-male method may have practical application for undesirable populations of certain wild animals as well as for insects."[539.5.2]

Eccentric Training: The Path to Power

Eccentric strength training as we now understand is the safest method to grow fast twitch fibers, and from Scot Mendelson to other elite powerlifters, its efficiency has been proven by sight alone. But is there something we're missing? Many years ago, while listening to a very obscure YouTube interview of Benedict Magnusson (One of the best deadlifters on the planet), Benedict mentioned that in the training period up to one of his record-breaking Deadlift days (I believe it was 1015LB), he began experimenting with a new form of training involving Eccentric-only Overload, where he would place the barbell in a rack from the height of a perfect lockout, load it with weights (most likely adding weight each set to go 10-30% beyond his 1RM), unracking it, and slowly lower it to the ground, then unload the bar, and setup again, no concentricity. He called these "Jet Deadlifts".

Remember that all forms of superslow training require extremely long detraining recovery periods to facilitate not only optimal, but adequate muscle and tendon repair. Many instructive videos on YouTube espouse the benefits of eccentric or superslow concentricity training, and demonstrate them in action, but neglect, quite ignorantly, the necessity of extended recovery periods, and in this error of omission and ignorance many people will become injured unnecessarily over time.

The FDA & Illegal Drugs

"As part of our comprehensive efforts, today we sent 12 warning letters and five online advisory letters to companies whose products, many of which are marketed as dietary supplements, are being illegally marketed as unapproved new drugs because the products bear unproven claims to prevent, treat or cure Alzheimer's disease, as well as a number of other serious diseases and health conditions, including diabetes and cancer. Products intended to treat Alzheimer's disease must gain FDA approval before they are sold in order to help ensure they are safe and effective for their intended medical use. Dietary supplements can, when substantiated, claim a number of potential benefits to consumer health, but they cannot claim to prevent, treat or cure diseases like Alzheimer's. Such claims can harm patients by discouraging them from seeking FDA-approved medical products that have been demonstrated to be safe and effective for these medical conditions."

-FDA Commissioner Scott Gottlieb, February 11, 2019

Think about the statement above for a moment, and then spend five minutes doing research on five to ten random phytochemicals—their effects on amyloid formation, or amyloid-induced neurotoxicity (Keywords: Dementia, Alzheimer's). You'll begin to notice the pattern that many commonly available phytochemicals are neuroprotective against neurodegeneration, and some are even capable of *reversing* the progression of neurodegeneration.

The fact that the head of the FDA in 2019 was so ignorant as to suggest that Alzheimer's disease is best treated with "FDA-approved" pharmaceuticals is morally irreprehensible. The FDA & Big Pharma will never suggest that EGCg nor or any other antioxidant be used to treat Alzheimer's disease, or any other progressive degenerative neurological condition, not because the phytochemicals aren't effective, but because they aren't profitable.

Where is the freedom in letting foolish & corrupt institutions control our supplement use, or even drug use? Why can adults legally get non-essential plastic surgery such as sex changes, breast implants, or rhinoplasty, which carries with them many risks, but ordering steroids or growth hormone from Asia is punishable by dozens of years in prison? I suppose bodybuilders and strength athletes are the true threats to a happy and safe society, and not pedophiles or rapists.

The Government exerts its strength through the justice system, and the justice system is full of insecure middle-aged men and women who love using the mind-altering drugs caffeine and alcohol to get "buzzed" but will ruin a man's life for possessing psychoactive mushrooms, anabolic steroids, or other *illicit drugs*—how obviously hypocritical they are. Now if you think the legal recreational chemicals the Government so graciously allows us to use are safer than illegal drugs, you are incorrect; Chronic Caffeine use increases impulsivity and moodiness, leading to bad decision making, especially in young adults. Concurrent Nicotine use without withdrawal leads to

dopamine burnout and apathy. Chronic Alcohol use is extremely neurotoxic and is often associated with the generation or exacerbation of psychosis and interpersonal issues, and this effect is only magnified during Alcohol withdrawal by Caffeine use.

It is my metapsychological hypothesis that these recreational drugs are legal only because they enhance work output (Caffeine = Task Switching, Nicotine = Working Memory, Alcohol Withdrawal = Enhanced Cued Memory), and that intriguing and potentially life altering psychotropic chemicals such as Psilocybin or LSD, or myogenic and lipolytic chemicals such as Anabolic Steroids or Growth Hormone are banned for general use because with greater mental bandwidth comes the comprehension required to overcome the cognitive dissonance that develops when we begin to question the efficiency and necessity of an ever-expanding government, and with greater physical prowess will come the confidence and youthful vitality to challenge tyranny with force. I do understand that many recreational drugs are useless for a brain (neurotoxic versus neurotrophic), and some are an "unnecessary risk", still I must argue that the issue of drug abuse is not a Governmental issue, it is a societal issue, and considering numerous commonly prescribed psychotropics approved by medical experts are as toxic, if not more toxic, on developing and matured brains, it makes no sense to selectively ban certain chemicals. Let the woman continue to take her Prozac, and damage her microbiome, and let the man continue to abuse THC, and damage his cardiovascular system, it is our job to give them the gift of knowledge, and allow them the choice to change their habits, not to imprison them, or confiscate their drug of choice.

In the future, if tyranny progresses, drug legality will be more intelligently regulated in favor of suppressing intelligent thought, such as when THC is no longer scheduled drug, leading to more frequent use, and abuse, damaging the brains of babies in utero due to their mother's addictive personalities, resulting in greater later life behavioral compliance to the Government, or a tendency to develop a mood disorder, or schizophrenia, and become slave to the pharmaceutical industry. This hypothesis is provided evidence by the fact that the Australian Government is now pushing for Nicotine to require a prescription for use, now why would a Government seek to ban a thoroughly researched nootropic, need I state the obvious? Nicotine is no more toxic to a developing or adult brain than alcohol or THC.

Even if our Health Institutions are simply incompetent, and not insidious, then why should we support them, why should we follow in their guidelines? Respect should be earned, and not given freely, and if incompetence is rampantly expressed from an authority, we must rebel against it.

Neurological Terraforming: A Freudian-inspired Hypothesis

I met a man once outside of a grocery store, and he told me that he enjoyed smoking Cannabis, and I argued that THC in high dosages is neurotoxic, but he replied that he was *Terraforming* his brain, leaving me with something to ponder.

Human beings will always inherently crave the use of chemicals that enhance Inflammation in the brain as they facilitate certain memory processes. But the real reason

why we as a species consume so much caffeine, nicotine, alcohol, and eventually legalized THC, is because through their respective use comes neurotoxicity, and through decreasing our neuronal populations comes a strengthening of specific memories and behaviors, thus making our jobs easier to perform, the strength of our love or passion for people, hobbies, & objects stronger, and our lives more predictable by reducing complexity of thought, especially the complexity of *expectations*. This is Neurological Terraforming, similar to the synaptic pruning that occurs during our childhood.

The issue arises when individuals with traumatic memories begin to terraform their brains, as memories containing unpleasant source material, especially ones formed during childhood, will never be dampened through neurotoxic drug use, because traumatic memories stored in Silent Engram Neurons are shielded from neurotoxic stimuli due to significantly less excitability, thus making them far more resilient to cell death.

"Being traces of experiences of pain, they have been cathected (activated) with excessively large $Q\phi$ (neuronal magnitudes) and have acquired an excessively strong facilitation to the release of unpleasure and affect".
[Pg. 381: Project for a Scientific Psychology]

"That the unconscious wishes always remain active is quite true. They represent paths which are passable whenever a sum of excitement makes use of them. Moreover, a remarkable peculiarity of the unconscious processes is the fact that they remain indestructible. Nothing can be brought to an end in the unconscious; nothing can cease or be forgotten. This impression is most strongly gained in the study of the neuroses, especially of hysteria."
[(d) Waking caused by the Dream—The Function of the Dream—The Anxiety Dream. The Interpretation of Dreams]

The proof of this general idea is displayed in that most mentally unwell individuals with traumatic memories who abuse drugs or are severely deprived of sleep (experiencing overt neurotoxicity), despite having a clear dysfunction in brain oscillations, have such vivid and accurate negatively emotionally charged memories upon recollection, memories which reoccur at a pathogenic frequency. One would assume the opposite would be true, that as neurons die, or brain waves are dysregulated, all memories would lose strength, both negative and positive, unhappy, and happy, but this is the opposite of the truth, as memories containing traumatic material only gain strength (activity: incorporation into consciousness) during neurodegeneration, or at the very least during dysregulated neural oscillatory patterns.

To overcome traumatic memories without catharsis, which as of now is unexplainable through documented mechanical science, is to promote bDNF expression—to grow new neurons, to form new memories, to create new *patterns* of thought. This is often accomplished through SSRI use, but serotonin receptors are rapidly desensitized, and SSRI's often carry with them unintended neurotoxic consequences. The only other option is antioxidant use, to quell the inflammation that psychological stress has caused and continues to cause, and protect the remaining neurons from destruction, or to promote

bDNF expression outright and enhance the malfunctioning system, that of which is known as our brain.

Unfortunately, the most human and common mistake is to pursue self-destruction, to continue to eliminate neurons, and to reduce complexity of thought, which only magnifies the suffering a traumatized individual experiences on a daily basis through flashbacks, or intrusive thoughts, due to a combination of synaptic dysfunction, neurite retraction, and neuron death.

A negative memory may be tamed, in Freudian terms, through a severe form of hypnotic therapy (catharsis), but for most the only feasible option is to run away from the predator that cannot be killed, that being their worst memories, and this requires the ever-increasing expansion of network connectivity through brain cell growth, allowing a negative thought or thought pattern to be weakened through the enhanced spread and activity of cortical activity through and near adjacent neurons.

Pain Relief & Drug Addiction

Treating chronic pain can be extremely difficult, firstly because the US Government is waging war on opioids, a war that started before Fentanyl use gained popularity, when Doctors began to feel the pressures of the hysterical anti-opioid push by the mass media, and federal law enforcement agencies. I see the war on opioids as being similar, but less morally reprehensible, as the earlier "war on drugs", specifically in relation to Marijuana.

The activation of the μ-opioid receptors in our brains results in an anxiolytic response, stimulates social behavior, and sometimes facilitates LTP[539.5.2A], suggesting that if an individual is capable of moderating their dosages, opioids are capable of exerting positive change in human life, but just like THC, we as humans have the insatiable desire to have more—to feel more, to go to the very farthest extremes of experience.

Marijuana strains are now four or five times more potent than in the past, and Fentanyl is nearly one hundred times more potent than morphine, but why is that? Well, Freud posited that many drugs, such as Nicotine (which stimulates the release of Oxytocin, a hormone released during the experience of love and after sex), are either replacements for sexual experience, or regressions to the familiar chemistry and safety of the womb.

The obsessiveness towards a drug an addict displays is not only because of a drugs addictive qualities, but moreso because the use of the chosen drug becomes a hobby, a passion, a love, or an artform (Notice the intricacy and science displayed in the vaping community), and most importantly, the chosen drug becomes a good friend, a replacement for something missing.

Stable and healthy drug users, such as the individuals who drink a cup or two of coffee every morning, treat their chosen drug as a facilitator of learning or creativity, and not as an escape from reality, and even if that chosen drug becomes a facet of their personality, because they have other hobbies, other vocations that provide them satisfaction and confidence, and other reasons to exist, they understand either consciously or

unconsciously that the purpose of life is to learn and to work—to strive towards comprehending an ever-expanding, ever-entangling amount of knowledge (complexity), and to strive towards happily exhausting themselves on a daily basis without complaint through what may seem to be innumerable repetitions in movement and speech i.e. building and maintaining careers and family lives, balanced by engaging in productive and innocent childlike hobbies.

But to explain the high prevalence of drug abuse in modern society we must take note of a few obvious contributing factors to drug addiction:

1. The vast majority of severely drug addicted individuals have too much time on their hands; they lack passions and vocations of productive and creative experience.
2. The vast majority of drug addicted individuals tend to have emotionally tumultuous pasts, not merely organic brain dysfunction, but instead a prehistory of psychological trauma.
3. The continued use of hard street drugs clearly predisposes a brain to addiction through a severe reduction in cognitive flexibility owing to concurrent neurotoxicity.
4. Severe drug addicts, the ones this essay is regarding, treat drugs as conduits of meaning.

The massive relapse among recently rehabilitated drug addicts proves that recovery is a much more complex and difficult process than we know. But in my analysis of rehabilitation, the steps I believe are necessary for success are as follows:

1. Rehabilitation clinics make the mistake of surrounding drug addicted individuals with other drug addicted individuals, which is the first mistake made during recovery, for we live and learn by example, and spending time around healthy minds is the first step to recovery.
2. Talk therapy is clearly of extreme importance, and many rehabilitation centers offer this, but counselling should not be conflated with therapy. To rush into counselling is to attempt to bypass catharsis, which is lazy and foolish psychological work done by psychological professionals. An individual with a traumatic history must be allowed to speak freely, and frequently, before being given platitudinous instructions.
3. Allowing a drug addict in rehabilitation to smoke and consume caffeine is counterintuitive to optimal psychological reconditioning, as all dopaminergic drugs must be barred, alongside any drugs which enhance impulsivity or reduce sleep quality.

4. There must be an effort to restore the brain of the drug addict to a state of proper health. Antioxidants should be administered, and a clean diet and an intense exercise protocol should be enforced.
5. Upon exiting rehabilitation, negative human influences must be excommunicated, such as drug abusing friends, or abusive family members, and in certain instances a move to a new city or state should be encouraged, as some memories are best overcome through escaping old environmental stimuli.

In closing, I am all for banning synthetic opioids such as Fentanyl which are unnaturally powerful, but are opioids our enemies? Surely not, for we are often the greatest enemies of ourselves. Whether an addict dies by alcohol-induced cirrhosis or cardiomyopathy, or a THC-induced heart attack or stroke, or respiratory failure due to opioid use, in the vast majority of cases it was not the drug that lead to their deaths, it was instead concurrent bad decision making—the incessant need to escape their current realities, compounded by genetic or psychologically-induced preexisting neurological damage. If we are to ban recreational drugs, such as "Gateway Drugs", we must begin with Caffeine, considering it increases impulsivity, reduces slow wave sleep, and is liable to cause or exacerbate many forms of drug-induced psychosis, it does not make sense to attack one or more drugs merely because they are socially acceptable, and associated with productivity, when they too can be abused and lead to an increased risk of relapse.

In the end, I must clarify that this new war on drugs is just a projected distraction from the deterioration of our society's morality stemming from the inefficient intergenerational parenting of children (sexual abuse, physical abuse, one parent households, selfish parents, and childhood bullying).

Altruism, Anthropomorphization, & Morality

Part One

Mirror neurons fire when we see someone else experiencing mental or physical discomfort, but their activation is not always associated with the generation of empathy, as context is important, such that a dying homeless person living outside a woman's apartment complex may seem more disgusting to her than sad but seeing an animal with a broken leg wandering the streets will elicit a strong empathetic response in her. But why exactly is it that *most* people, would sooner help an injured animal than an injured human? What happened in our evolutionary prehistory to lead to such pronounced unhealthy anthropomorphizing behavior? Well, by using logical reasoning skills we can come to a sensible conclusion; If ancient animal owners used their dogs and cats for survivalist purposes, such as hunting, foraging, or home protection, we find a reason for the development and facilitation of canine and feline relationships. But 21st Century animal owners do not own their pets for essential purposes, they merely

anthropomorphize them, they treat them like babies or young children, and it can therefore be said that they are using animals as a way to emulate parenthood in a very immature way, considering pets are much easier to take care of than children, this would explain why many women, and certain men, treat animals with such reverence, because they unconsciously associate them with children or other human family members. It is true that pets are often a cure to a lonely human life, but that does not change the fact that they are *substitutions* for human connection, and pathological substitutions at times.

The Terminal Investment Hypothesis (TIH) suggests that when an animal, primarily female animals, are nearing death, they invest significantly more energy into reproductive efforts to ensure their genes are passed on. I believe TIH is applicable to willingly childless adults, where after reaching a certain age, begin to anthropomorphize their animals to a pathogenic level, and often adopt new pets. Now, is it wrong of me to criticize how a person's love is dispersed? Possibly, but I am not criticizing their behaviors because I dislike animals, I am criticizing them because Anthropomorphization is inefficient and unhealthy, it is simply deranged to respect and love lesser animals more than human beings. To hide within your home seated alongside your chosen pet, while binge watching Netflix, and biologically decaying is, in my opinion, a waste of life. Our time on Earth is precious, and taking care of a lesser animal could be better spent raising an actual child, exercising, traveling, learning, volunteering, or partaking in an intellectually demanding hobby. I do understand that dogs and cats are conscious, and that they can offer us affection, but this form of love is not conducive towards intellectual growth, it is merely an inefficient treatment for human insecurity, to become the caretaker of an animal whose entire world revolves around you—you of whom are in effect, their mother-father, and if you do not consider your pet lower than you in intelligence, power, and worth, your grasp of reality is that of a child. Furthermore, why are we obsessed with preserving the life of dogs and cats, and yet kill the spiders, bees, and ants that enter into our homes? They are conscious too; do they deserve to die merely because they are "ugly", not "cute", or not capable of experiencing or displaying complex emotions? This selective morality of an obsession with "cuteness" is more evidence to the pathologically expressed psychological displacement present in animal rights advocates who are predominately females, or emasculated men, and in those who adopt and spoil their animals while neglecting their human children.

To reiterate, I do agree that having a dog, cat, or another emotionally expressive animal as a pet may soothe a troubled or lonely mind, but there are still far more interesting and profitable things to spend our time doing in our short life on this planet, and I am far more disturbed by the morality of outspoken animal rights advocates than antisocial homebody cat people who are likely to suffer from Toxoplasmosis.

Anthropomorphization is not simply an illogically inert phenomenon of wasted human potential, it is dangerous because it propels humankind towards falsely attributing human-like consciousness to AI's, which will never reach sentience, not to mention the

eventual normalization of Chimeras. The people who dress up their dogs and cats in cutesy outfits and speak to them as if they understand English, are the same people who will destabilize the world in the distant future when they marry their AI-Automatons, protest for AI rights, or support the creation and autonomy of Chimeras. For if you consider your dog to be equal to you, why would a superintelligent but devoid of consciousness robot that can accurately analyze your verbal infections, microexpressions, and manipulate your moods not be considered as an equal also?

In closing this part, I must say that the continual push and growing popularity of animal rights movements, and by relation, climate change movements, are the most embarrassing types of feigned altruism possible, for over 800 million people, many of them children, are starving, or massively malnourished on this planet currently (2025), and these human beings need protein to grow, to survive, they need animal meat, and to suggest that they be airdropped low protein expensive-to-produce imitation meat made of estrogenic soy or dystopian-like bug protein bars is both asinine and evil. Many people suggest that global poverty and hunger can be solved if we all just work together but there is no possibility of rapidly and efficiently diverting economic resources to accomplish a worldwide goal, that's not how life works, and considering our human population continues to expand, to end starvation & hunger, and eventually other issues such as homelessness, would require the world building stratagems of a being that does not suffer from the human condition. It is true however that if even a tiny portion of the world banded together to form and operate altruistic organizations, the majority of suffering on this planet could be quelled, but even for the organizations that exist, there is a striking lack of volunteers and donations, and this is explained by the deranged empathy processes of the next generation of moral warriors, who choose to fight for causes that require little to no effort (protesting politics is far easier than volunteering at a foodbank), but which still give them a sense of religion-like contentedness, and who assume falsely that the Government (The Father of Materialism) is capable of solving all moral (Psychological / Spiritual) crises. If you are a misanthrope, and prefer the company of dogs, cats, and other animals, and you are honest and conscious of this, you are respectable, even if you are suffering from some serious psychological issues, but if you claim to be a good person while never positively effecting another human beings life beyond a smile, you are more misguided than the former cause.

Part Two

Children who are taught *morality through human altruism*, such as when parents bring a child to volunteer with them or engage in altruistic human-human deeds with adults generally develop emotional processing centers that are ideal, ones that are capable of bettering a society, these children often grow into citizens capable of effecting positive change in the world, and that positive change is a reduction in human suffering, which must come before lesser animal suffering, and "environmental suffering". Children who are taught *morality through diet* & *morality through animal altruism* will be much more

likely to develop deranged emotional intelligence centers which will lead them, if they believe in no God, to seeking meaning in a chaotic force that is completely irrational; Green Energy, that of which often pollutes the environment more than its alternatives and requires technological evolution and expansion to function (greater pollution). Why do the most ardent supporters of preventing or mitigating human-made climate change and pollution use smartphones, or drive Tesla's, which have lithium ion batteries that poison ground soil when discarded into landfills[539.5.3] or those who recycle waste such as plastics, which only contributes to the cycle of toxic plastic particles accumulating in our blood from food and drink packaging and the poisoning of the ocean[539.5.4]. It is precisely because like all religions, the belief in Green Energy is delusional, it requires irrationality to function, it requires *faith*, and more importantly it is a veiled disguise for technology worship, the unspoken and unconscious religion of Transhumanism. The underlying issue with transhumanism, aside from the obvious inevitable loss of our connection with the true reality after the advent of cyberspace, a realm that will one day be dominated by one or more nefarious forces, is that the coexistence between Earth and Technology will require far more evolved and intelligent forms of renewable energy and recycling technology, ones that we do not currently possess or utilize. Our form of transhumanism comes not from the desire to mend the ill and disabled, to provide nerve-linked artificial limbs for amputees, or to provide technologically-stimulated muscle control to the paralyzed, the form of transhumanism we embrace comes from a selfish place, and because we treat technology as a way to climb the pecking order, to compensate for our fragile Ego's, and to attempt to live forever, the greatest medical innovations that our transhumanism will inevitably result in will be repressed, and delayed, as they are today, where we can find intellectually and creatively superior scientists who have hypothesized on novel ways to strengthen the weak and forgotten in our society, but who have been and will continue to be rarely provided the proper funding or attention to bring their ideas to fruition. Are the hundreds of millions of US dollars that go towards funding Gender studies annually more necessary to a societies wellbeing than providing funding with the aim of healing and regenerating the human beings suffering from dementias, paraplegias, and visual-audio disabilities? Is unending sexual revolution and sexual obsession a greater healing force than directed sublimation, and scientific innovation?

Most toxic and substantial forms of pollution derive solely from technological evolution, not merely from overpopulation. Humorously, the elites will say that we can save the planet by reducing overpopulation, while assuming unjustly that their lives are more meaningful than that of a starving African child, and they spew overpopulation platitudes all the while magnifying their "carbon footprint" by engaging in the highest levels of consumerism. If you believe overpopulation is the greatest threat to the human species, you would make a good gain-of-function researcher.

The true believers in Mother Earth embrace luddism and retreat to the wilderness, and for that they have my respect, but I pity those ignorant enough to believe that technology and the mandates for technological use enacted by an overreaching Government and large

profit-focused Corporations can solve all environmental issues, especially the problems they create.

Technology is not a tool used by humans to simply make their lives easier, it is a tool wielded by humans to give them more power—the power to save lives, the power to take lives, the power to attain knowledge, the power to fulfill libidos (both carnally and intellectually), and the power to accrue wealth. And in this power comes the addiction to harness complexity (emergent phenomenon) for not only our survival, but for our profit, and when selfishness supersedes survivalism and is not balanced by altruism man begins to lose his humanity.

Part Three

As an addendum, a more common and interesting hypothetical result of bad parenting, aside from the development of psychopathy in children, would be a mental disorder not currently classified in any DSM, and therefore I would term it *Delusional Empathy Disorder* (DED) and consider it more contagious for a society than psychopathy because it is insidious and therefore spreads among all strata's of society unnoticed. It is a condition that develops in children raised by parents who would rather go out and drink with their friends, play video games by themselves, or endlessly browse TikTok videos and watch Netflix shows (slaves of dramatism), while secluding their children to the parental supervision of a televised or internet dreamworld. These children then develop illogical and unhealthy mirror neuron activation patterns as their morality is formed from cartoons, and fantasy, rather than from parent-child intellectual discussions on life and all its harsh complexities (a hallmark of good parenting), leading to fully grown adults *crying* when fictional characters die in movies or TV shows which is an all too common and clear display of a malfunctioning or immature emotional system most often seen in children, but now openly and proudly displayed by adults, because their surrogate parents become their fictional superheroes, antiheroes, or even their favorite villains.

It is unfortunate that children are no longer raised by their parents, they are raised by other children, and by overworked teachers, they are raised by fictional hyperemotional media. In terms of developed nations, a child who is homeschooled is much more liable to possess an evolved morality as compared to a child who spends all day and night surrounded by their chaotically immature drug-abusing contemporaries (vaping, THC-use), because the play and sport children engage in today is far different from the past, no longer do they play with sticks, and stones, and roleplay creatively as heroes, or villains, they instead hide away within their rooms, attempting to form and maintain close but extremely distant relationships, and they consistently absorb more and more regressive humor and perverse material (look at the Snapchat spotlight feed for evidence of this). To give a young child unfiltered access to the internet while simultaneously neglecting them of parent-child intellectual bonding experiences is to destroy a portion of their potential, to make them pathologically associate sincerity with the non-existent, and insincerity with what they consider an inferior base reality, it is to blind them through blue light.

Attempting to escape reality through fiction is sometimes therapeutic but it is also a pathological addiction that goes unnoticed. The life, matter, and thoughts that exist on our planet, and beyond it, are so interesting that we have had to form so very many different scientific disciplines, and I believe in an ideal society each human would specialize in one specific science, to continue to unravel the mysteries of the world, for the unconscious mind can be harnessed to continue to evolve science, and not merely to dream of and worship the same types of god-figures (superheroes) that our ancestors use to, the half-men, half-animal mythological gods of old, and future gene-spliced abominations. If each man and woman found a science to embrace, any intelligent science, from ones involving human health to the study of space phenomenon, we would no longer be ignorant to the wonders of life, and there would no longer be a disparity in respect between the technocratic elite, and the laymen, the college educated and those they perceive as inferior. Many are fooled into believing that the study of science or any branch therein requires a high level of brain connectivity to achieve success, but that is only the case for more mathematical branches of science, as many others only require simple visual observation, and elaboration, and success in science does not always mean earning a Master's degree and profiting from your studies, it means that you have formed a passion in attempting to understand the world around you, whether that be from classifying the plant life that grow in your lawn, to understanding the lifecycle of the spider that adorns your house with its webbed majesty, to comprehending the complexities of human muscle contraction, we must strive for knowledge and wisdom or we will lose our connection with the true reality we reside in. Creative thought should be directed towards the branches of science, not only the hysterical and often delusional works of fiction, but it should be refined through analysis and critical appraisal.

Plastic World

Note: I am categorizing this not as a section but as a micro-essay because I do not believe dietary plastic particles pose a great risk to our health currently, not compared to VOC's, Heavy metals, and other environmental toxins.

Plastic particles accumulate in our bloodstream when we consume food or drinks stored in plastics[1], these "microplastic" particles leach from the packaging materials during the processing and storage of consumables. One of the mechanisms that plastic particles are able to pass the Blood Brain Barrier is through binding to cholesterol molecules[2], highlighting the strange toxic synergism of ultraprocessed foods.

Although the toxicity of plastic particles is not to be considered severe currently in humans due to the low concentrations of these particles in our bodies, it is logical to predict that if plastics continue to be used in the processing of consumables, and beauty products, a future generation of humans will accumulate enough nano/microplastics to exert neurotoxic or pro-dysbiosis effects.

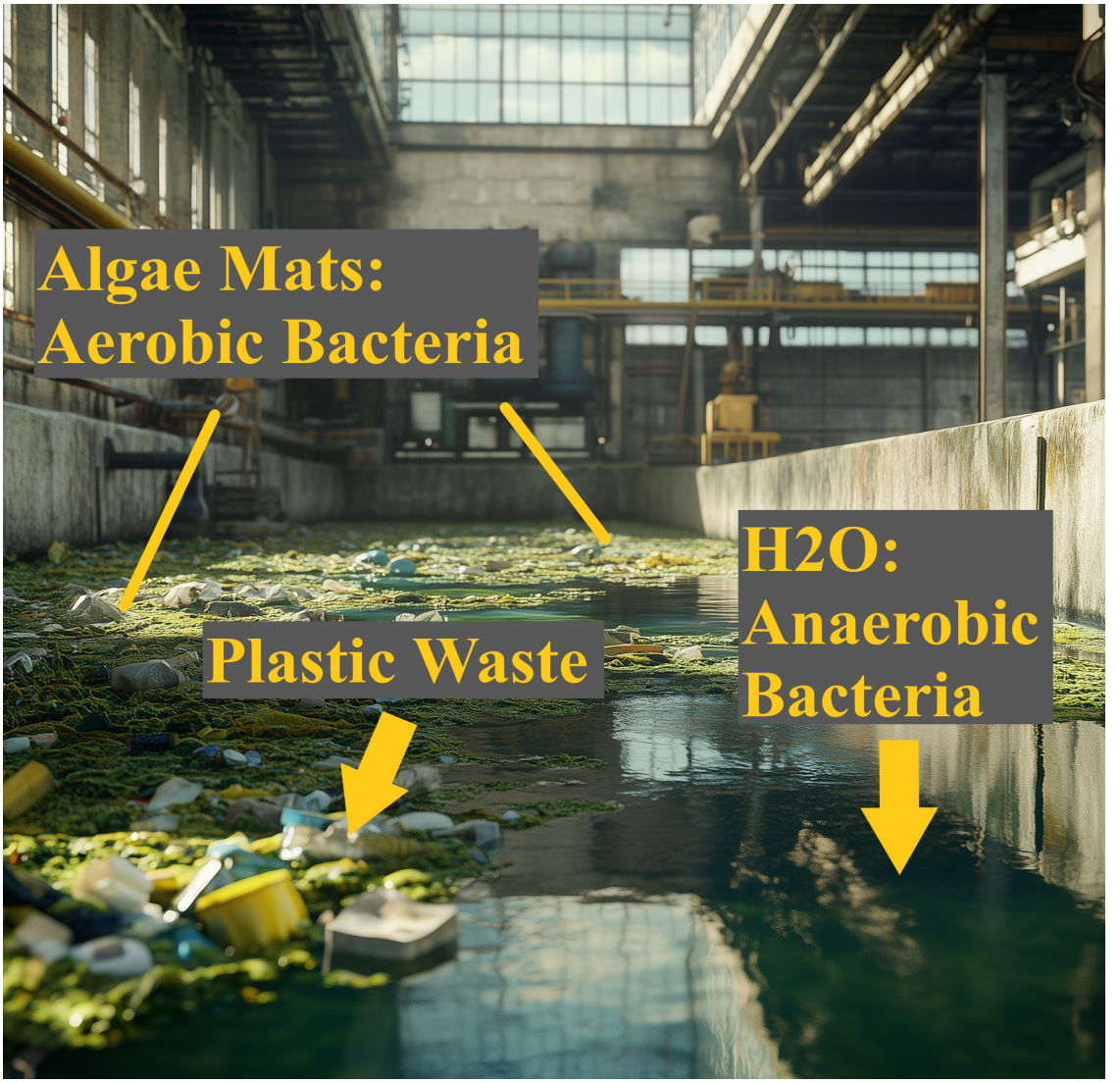
Bisphenol-A (BPA) is a chemical used during the formation of plastics that has been demonstrably proven to have estrogenic effects[4], and although the anti-BPA push by the general public is beneficial, it does not solve the real threat, which is plastic particle accumulation in the body, as it is my hypothesis that the evolutionary purpose of plastic particle accumulation in our bodies and on Earth is not to directly damage our health or the health of the planet, but instead to terraform all organic life through *Plastic Particle Interfacing* (PPI), a term I coin to describe this future dystopian technology I predict. Firstly, plastic particles in our bodies will render our organic tissue slaves to Big Governments and their Artificial Intelligences, as microplastics will easily be synced to injected nanodevices[539.5.5] which will allow 24/7 monitoring of movement, as cameras on every street corner will not offer enough information on citizen movement or behavior. This will be possible once the nanodevices are *injected* into the body & bind to microplastics stored in different tissues, because microplastics show a tendency to accumulate heavy metals and thus will easily bind to or allow anchoring of metallic nanodevices, which will begin to transduce signals that will be transmitted from the body to external receivers, or within the body to our Neural implants, where they will transmit scrambled encrypted signals along cyberspace channels.

Secondly, at a later point in time, a Synthetic Intelligence will possibly find use through PPI to not only monitor human beings but alter their physiology, and directly control ecosystems in nature.

One may ask why nanodevices would require plastic particles to operate, and clearly the answer is they do not, but plastic particles will offer superb camouflage for nanodevices because they are so ubiquitous in the body, and because they enter into systemic circulation through diet and pass through the BBB, they are therefore to be considered *Technological Extracellular vesicles*.

Interestingly, surveilling human movement internally and constantly with nanodevices bound to microplastics, when combined with Neural implant monitoring of brain activity, will lead inevitably to predictive analytics being embraced by future governments to form Pre-crime units, such as in the movie Minority Report. For anger is surely to be quantified through subtle brain wave, speech, & movement pattern analysis of individuals allowing AI's to accurately (but not perfectly) predict crimes before they happen.

The only way to combat a "Plastic World" from forming *locally* in my hypothesis is to use microbes to consume or degrade microplastics—to create landfills, or even better, lakes, which are continually cultured & replenished with specific organisms capable of breaking down plastic waste[3], there is also the possibility of creating plastic treatment plants. As for other forms of waste, Upcycling is far more beneficial than recycling, because recycling often produce more pollution than the original product produced in the first place. Through private industry, and possibly but inconsequentially, government incentives, these hypothetical Plastic-degrading Microbe Reservoirs could become commonplace.



Regarding Upcycling, of reusing or reforming potential waste not through thermal or chemical treatment, but through repurposing or reconfiguring waste to be used and enjoyed through a secondary consumerism, it is the most intelligent and effective form of recycling. It is not often embraced by Eco-Warriors because they are still slaves to the allure of novelty and affluence, quite hypocritically. But buying used products or creatively repurposed Upcycled products is an excellent way for an intelligent human to reduce the accumulation of toxic waste on our planet. Of course, there is no point in attempting to halt global plastic manufacturing as the progress towards the formation of a Plastic World is inevitable, we can however control our cities health through the creation and enaction of what I call *Microbe-based Plastic Degradation Methods* (MPDM). Unfortunately, these novel waste disposal methods will not be able to keep up with the current and the ever accelerating plastic waste that results from consumerism, but I predict there will be certain cities that eventually embrace the true powers of nature and her tremendously impressive microscopic life through MPDM, such as with specialized lakes, reservoirs, or processing plants, and we may even find backyard cultured ponds in

wealthy districts where people discard their plastic waste accumulated through unending consumerism.

Recycling Plastic is inefficient, toxic, and not worth its energy and manpower expenditure, because of the complexity of plastic polymers, they only degrade during recycling processing leading to the creation of inferior end-products. Recycling metal products is far more efficient, and requires far less energy to accomplish, meaning that you should absolutely attempt to recycle aluminum cans or other metal waste that accumulates during everyday life, but save the plastic products for Upcycling, or a landfill. Strangely, for many, it's not really about the environmental impact of waste, it's about *feeling* like a good person, for they will say "I recycle" therefore "I am saving the Earth", while they continue to embrace consumerism and hypocritically pollute the planet in numerous other ways, seemingly oblivious to the true impact of their "Ecological Footprint".

[1] "<>Plastic particles are ubiquitous pollutants in the living environment and food chain but no study to date has reported on the internal exposure of plastic particles in human blood. This study's goal was to develop a robust and sensitive sampling and analytical method with double shot pyrolysis - gas chromatography/mass spectrometry and apply it to measure plastic particles ≥700 nm in human whole blood from 22 healthy volunteers. Four high production volume polymers applied in plastic were identified and quantified for the first time in blood. Polyethylene terephthalate, polyethylene and polymers of styrene (a sum parameter of polystyrene, expanded polystyrene, acetonitrile butadiene styrene etc.) were the most widely encountered, followed by poly(methyl methacrylate). Polypropylene was analysed but values were under the limits of quantification.
<>In this study of a small set of donors, the mean of the sum quantifiable concentration of plastic particles in blood was 1.6 μg/ml, showing a first measurement of the mass concentration of the polymeric component of plastic in human blood. This pioneering human biomonitoring study demonstrated that plastic particles are bioavailable for uptake into the human bloodstream. An understanding of the exposure of these substances in humans and the associated hazard of such exposure is needed to determine whether or not plastic particle exposure is a public health risk."[539.5.6]

[2] "<>Humans are continuously exposed to polymeric materials such as in textiles, car tires and packaging. Unfortunately, their break down products pollute our environment, leading to widespread contamination with micro- and nanoplastics (MNPs). The blood–brain barrier (BBB) is an important biological barrier that protects the brain from harmful substances.
<>In our study we performed short term uptake studies in mice with orally administered polystyrene micro-/nanoparticles (9.55 μm, 1.14 μm, 0.293 μm). We show that nanometer sized particles—but not bigger particles—reach the brain within only 2 h after

gavage. To understand the transport mechanism, we performed coarse-grained molecular dynamics simulations on the interaction of DOPC bilayers with a polystyrene nanoparticle in the presence and absence of various coronae.
<>We found that the composition of the biomolecular corona surrounding the plastic particles was critical for passage through the BBB. Cholesterol molecules enhanced the uptake of these contaminants into the membrane of the BBB, whereas the protein model inhibited it. These opposing effects could explain the passive transport of the particles into the brain."[539.5.7]

[3] "<>Microbial diversity is the key condition for biodegradation. Microorganisms include bacteria, fungi, and a few algae, which have powerful functions and abilities, such as small size, fast absorption, and metabolism, strong adaptability, easy variation, and wide distribution. Microorganisms have congenital or acquired abilities to survive even in places with particularly harsh environments. The microbial communities can adapt to new environments and attach to them, and they mainly release certain enzymes that allow them to utilize persistent plastic pollution as their only carbon source. Biodegradation is influenced by a combination of biological and abiotic factors.
<>Biological factors include bacteria, fungi, biofilms, and microbial communities as the carbon source food for microorganisms. Abiotic factors are from several aspects of natural photooxidation and man-made physical and chemical degradation. These factors catalyze complex metabolic reactions to form the ecosystem structure and function of biodegradable plastics. The microbial degradation of plastics and MPs is affected by the growth of microorganisms and factors related to the external environment. Environmental variables and the habitat under study may be major determinants of microbial diversity and richness. In addition to the microorganisms involved, the circumstances for plastic biodegradation also depend on the surface properties and surface structure of plastic materials, such as roughness, electrostatic interaction, topography, hydrophobicity, and free energy.
<>More possibilities for effective biodegradation of polymers involve various microorganisms. In marine habitats, biofilms formed by microbial populations are conducive to plastics and MPs degradation. The formation of microbial biofilm is the way of polymer biodegradation. It is initially attached by microorganisms and forms microbial biofilm on the surface of the plastic, which is called a plastisphere [30]. Microbial communities are associated with biofilms. The biofilms contain different microbial communities and contain potential plastics degrading microorganisms. For instance, the hydrophobicity of PE interferes with the formation of biofilm. However, the micro-bacterial community with high cell surface hydrophobicity can better adhere to the surface of PE and form biofilm on its surface.
<>In nature, however, various studies have shown that the bacteria typically collaborate in communities. The microbial community has a variety of microorganisms to participate in the degradation, which improves efficiency compared to a single microorganism.

Microbial communities or consortia can degrade complex compounds into single monomers due to the observation of multiple microorganisms that coexist in an environment to function together.
<>The pure cultures of bacteria isolated from most environments show that bacteria have diversity and functionality. Through the identification of a large amount of data, species belonging to various bacterial phyla, including Proteobacteria, Firmicutes and Actinobacteria, are able to degrade plastics. Most potential bacteria that can biodegrade plastics were isolated from contaminated sites, such as landfills. Based on bacteria's inherent ability to break down long-chain fatty acids, plastic degradation is possible. Bacterial species from Pseudomonas, Escherichia, and Bacillus genera exhibit enormous potential for degrading plastics, especially for recalcitrant polymers, such as PE, PET, PS. Additionally, it has been demonstrated that bacterial strains, such as Pseudomonas aeruginosa, Bacillus megaterium, Rhodococcus ruber, and others may break down the thermoplastics PE and PET. Furthermore, fungi able to degrade plastics have a powerful enzymatic system. Filamentous fungi play an important role in the degradation and mineralization of plastic pollutants. They have the ability to degrade PE and PET. With more research, it was discovered that microorganisms able to degrade plastic vary in the diversity, abundance, and activity, providing plastic-degrading evidence."[539.5.8]

[Preemptive Retort: To those who consider my idea of PPI as unrealistic, you should study nanobot advancements before you criticize my thoughts]

Pressing & Rowing with Ulnar or Radial Deviation

Wrist lateral flexion / yaw (pinky>wrist = ulnar deviation, thumb>wrist = radial deviation) is not often thought of when performing upper body work and although I don't necessarily think changing yaw drastically effects muscle activation, and may even increase the risk of injury, it is still an interesting idea for exercise variation to incorporate into your workout routine with *lower loads*.
When performing pressing exercises with ulnar deviation the pectorals are activated to a greater extent, conversely when performing pressing exercises with radial deviation, the triceps are activated to a greater extent, as for upper back muscle activity during rowing, when ulnar deviated the teres minor and major are activated, and when radial deviated the rhomboids and lats are activated.

To experiment with wrist yaw exercise variations, consider using the Titan Yukon Bar for Ulnar Deviated bench pressing, and a rackable (long) Rogue EZ Bar for Radial Deviated bench pressing or rowing.

Seasonal Thermal Therapy Cycling

On average in the northern hemisphere, three months of the year are the hottest, and three months of the year are the coldest. This is a natural cycle of weather and should be utilized for its thermal benefits and convenience. To fully take advantage of the natural climate changes that come and go each year, you should first begin *acclimating* yourself to exercising outside.

During the hottest months of the year, the hyperthermic, you should engage in high intensity cardiovascular exercise, or bodyweight resistance training. In the summer months you can magnify the heat accumulation in the body by wearing a sauna suit or a very thick fabric sweatsuit.

During the coldest months of the year, you should specialize in steady-state cardio or aerobics. Traditional Cryotherapy is expensive, and not very effective, and the frequent use of home ice bathes are too expensive for most, but the winter months offer us the perfect chance to use the cold weather as the most economical form of hypothermia therapy, in that we can go for walks in very little clothing, or swim in iced over lakes.

There may be some scientific merit to the periodicity of seasonal weather change in relation to ancient man's metabolism, myogenic potential, and lifespan, such that there may be a naturally defined limit to cellular adaptation from thermal therapy; Three months of hyperthermic summer anabolism, three months of hypothermic winter catabolism, and four months of no thermal therapy. An all-encompassing routine similar to this would make sense considering all thermal therapies carry with them unintended side effects.

The Placebo Effect

In science, the body predated the formation of the mind, but in religion, the mind predated the formation of the body. How do we explain how the mind is capable of overcoming signals emanating from the body, to overcome pain? One may argue that the propensity of human beings to engage in delusional thinking succinctly explains the phenomenon of the placebo effect, that it is in our nature to overpower our bodies through thought alone, to subdue them, for the sake of survival. I am more of the *belief* (pun intended) that this strange psychological phenomenon is a survival mechanism.

But if certain cases of depression are an evolutionary adaptation to protect our immune system, would that not conflict with the idea that the placebo effect confers pro-survival evolutionary benefits by enhancing mood, and promoting sociality? I think it is logical to suggest these forces do not actually conflict, but instead overlap, as the placebo effect is both a *post-sickness reactive phenomenon*, and *pre-sickness reactive phenomenon*, meaning that the placebo effect is physiologically and psychologically beneficial in individuals who are either healthy or sick / injured, and is most often a form of delusional thinking that occurs daily during conditioned behaviors to attempt to silence certain negative thoughts, such as when people falsely assume by taking one multivitamin tablet they are preventing malnutrition, or when people falsely consider drinking a cup of coffee

each morning to be essential to the success and productivity of their days. The placebo effect, or conditioned optimism, is used every day by nearly every human being.

Now it can be said that many people have an innate disposition to optimism, and this could be due to neurotransmitter differences, or receptor dynamics, but a disposition towards experiencing a psychological phenomenon is not a prerequisite to experience a psychological phenomenon, such as optimism, and therefore we cannot make the claim that the placebo effect is intricately tied to religiousness, nor mental illness, as even the most rational and atheistic individuals utilize it to comfort themselves.

If research continues to prove that the mind is capable of directly albeit subtly changing physiological parameters, such as blood pressure, or immunological indices, then the placebo effect could be explained as one way for the brain to enhance the fitness of the body by reducing stress or the sensitivity to internal or external stressors, because in the case of the most studied placebo effect (medical), many forms of chronic sickness or pain do not result in expedited death but regardless reduce longevity and the prospects of reproduction owing to negative changes to physiology first, and behavior second.

Delusional thinking in regard to the placebo effect is often beneficial to the host but may lead to an acceleration towards death often due to a form of illogical medical *hyper-optimism* i.e. “my doctor told me to jump off a bridge to treat my bad back, so I did” so said the missing elderly man who reveled in the presence of his earthly biomedical priest every six months, or the man or woman who takes one multivitamin tablet per day and suggests they are health proofing themselves. Conversely, a life without waves of optimism will be much shorter, and unsatisfying, due to the magnification of physical and psychological pain from hyper-rationality and the resultant facilitation of *hyper-pessimism*, where the belief in good outcomes, and any beneficial internally generated physiological change due to positive thinking becomes nullified by the constant expectation of uncertainty and of socio-environmental chaos, such as the expectation of human ignorance and malevolence, which is sure to stimulate premonitory stress hormone release, and therefore promote accelerated cellular decay.

Nature’s Remedies vs the God Complex

To restore the neurological and psychological health of a patient suffering from any form of Dementia will require not only the targeted use of phytochemical extracts and variegated unapproved therapies, but in many cases due to patient locality, the approval of a physician who is overseeing the care of your sick friend or family member, *for they will be your greatest obstacle in treating your loved ones*, they will suggest the research contained within this book is untested, or dangerous, but is the end result of dementia not death regardless? We have the power to control our lives, and we can also heal those around us, if we possess enough courage and intelligence to *apply* the breakthrough research available to us. Do not be afraid then to take any and all steps to save the life of those who suffer forgetfully in fluorescent corridors—the prisons of emotional convenience that allow the progeny to forget willingly of those who gave them life.

If you have bypassed the tyrannical medical control over your loved one, or if you or a friend or family member is actively taking care of one suffering from any of the varied Dementias, your second obstacle will be to change the sick individuals diet, to restrict their carbohydrate intake and their Palmitic acid consumption, this is of the utmost importance.

The third obstacle in restoring your loved ones consciousness will be the complexity of administration (of herbal extracts predominately). This will be a difficult if the sickly individual is stubborn, moody, or dissociated, and if they have trouble swallowing it will be even more difficult. Your best option therefore is to begin with Essential oil therapy. Rub a blend of Essential oils under their nose four or five times a day and tell them to breathe only through their nose for a few minutes after application, spray the front of their shirt with this same blend multiple times a day, and rub a safe and powerful TALM into their feet every morning and evening, you can't go wrong with Eucalyptus Globulus oil, East Indian Sandalwood oil, and Lavender Angustifolia oil. After they show a noticeable improvement to memory or mood, you can begin the administration of your neuroprotective compounds, either by way of capsule, tablet, or liquid. Remember that EGCg and Quercetin are commonly sold, popular, and potent anti-dementia compounds that protect the brain from beta-amyloid, tau, and a-synuclein.

The fourth obstacle in this scenario is exercise, many elderly people do not have energy to exercise, not only because of a bad diet, but because of a lack of hormones. If you were to administer to them significant amounts of DHEA, it may counteract this deficiency to an extent, but they will have to be forced through verbal coercion to exercise intensely every day on a cardiovascular apparatus, such as a recumbent bike, which is ideal for the promotion of neurological rehabilitation in not only dementia patients, but also epilepsy patients due to its comfortable seated positioning and high level of safety (My favorite is the Sunny Fitness SF-RB424002). Although high intensity cardiovascular exercise is the most neuroprotective form of cardio, you should begin their workout protocol with injury prevention, and maintainable intensity in mind, such that they will perform 60% Max HR x 30-Minutes per day, and eventually moving up to 60-Minutes per day, and when their leg muscles have been conditioned and grown safely, 70% Max HR x 30-Minutes three or four days a week. I understand money does not grow on trees, but if it be necessary that you invest in an exercise bicycle at home, so be it, is there a price on your loved ones life? And if you are impoverished financially, seek a loan.

If you succeed in actuating and facilitating an effective neurological rehabilitation, no medical professional will believe that you accomplished such a feat, they will more than likely gaslight you and your now fully conscious loved one into believing this recovery was a result of a natural homeostatic mechanism unrelated to love, diet, herbalism, or exercise, and they will suggest that their neurological condition was not as serious as the medical imaging or behavioral effects had indicated, and when this happens you will come to the revelation that the power nature offers you is uncorrupted by Ego.

Recognizing Flawed Study Designs

I feel it necessary to aid the readers of this work in being able to distinguish good research articles from bad ones. Bad studies suffer from flawed study design, that of which leads to false conclusions.

The most common flawed studies you will encounter are firstly ones that inadvertently reach conclusions without considering all of the variables present, such as studies involving two chemicals that reach a hyperbolic conclusion, and ones involving human testing. Secondly are studies on phytochemicals that are contained within plants that grow locally in the researchers' home countries. In these studies, we may find nationalism bias in reached conclusions and must be cautious in interpretation. Thirdly, studies that are paraphrased and reworded copies of previous studies are very common, in fact I would venture to guess that over a third of all PubMed articles are redundant and embarrassingly obvious plagiarism, or worse, fabrications, primarily originating from Chinese researchers[539.5.9].

One clear example of *conflationary* flawed study design is the research on Magnesium L-Threonate. Why do barely any of the studies on this new magnesium formulation mention that L-Threonate (L-Threonic Acid) is merely a byproduct of Ascorbic Acid metabolism? Probably because Ascorbic Acid happens to be one of the most inexpensive antioxidants that can be purchased on the internet. Are the supposed neurological benefits of Magnesium L-Threonate coming from Magnesium, or L-Threonic Acid?

Here are three important tests for you, the first two are research article abstracts I created containing numerous study design flaws, and third is an actual study on the adipogenic effects of Cinnamon. You should attempt to figure out through cursory analysis why these studies are to be considered illogical and misleading in their conclusions and then see Page 1135 for answers.

[A] Study 1.

"<>Background: We have taken the initiative in attempting to elucidate the connection between high intensity exercise intensity and cardiovascular health.
<>Methods: In this study we recruited twenty male and female adults without documented chronic health conditions, and who testified to exercising less than once per week. Blood was drawn from the participants before & after the trial to measure serum triglycerides. The participants were between the ages of 20-65. The exercise procedure was a XYZ-9000 recumbent bike, with a resistance level set at 5. The participants all warmed up by cycling on the recumbent bike for twenty minutes at a level of 2 before beginning the active study. The participants were then told to cycle as fast as possible for a period of forty seconds, followed by a rest period of three minutes, and this was repeated six times. Heart rate variability was accounted for by age. Any participants who were unable to reach an 80% or higher heart rate based on age-respective predictions in maximum heart rate were excluded from the results.

<>Results: The post-workout bloodwork of the participants of this study showed average decreases in triglyceride count, averaging around 4%.
<>Conclusion: We conclude that high intensity exercise is beneficial to decrease triglyceride levels, but that this effect is not statistically significant.[!?!]

[B] Study 2.

"<>Background: We have taken the initiative in attempting to elucidate the connection between the consumption of Green Tea and blood glucose.
<>Methods: In this study we recruited twenty male and female adults without documented chronic health conditions. The participants were between the ages of 20-22. The participants were all administered 4,000mg of Green Tea Extract mixed with water sourced from Sigma-Male chemicals. Blood was drawn from the participants immediately before & thirty minutes after consuming the extract to compare blood glucose.
<>Results: There was a 25% average decrease in blood glucose which is a statistically significant effect.
<>Conclusion: We conclude that the polyphenols in Green Tea exert an anti-diabetic effect and may be used in the general population to decrease blood glucose.[?!?]

[C] Study 3.

"<>Objective: Cinnamon is a cooking spice and a medicinal herb. It is increasingly used as a health supplement due to its perceived benefit to prevent and or manage type 2 diabetes and metabolic disorders. However, it is unclear if regular consumption of this medicinal plant will interfere with normal physiological functions. Therefore, this study investigated the impact of daily cinnamon supplements on glucose and lipid metabolic profiles in healthy rats.
<>Methods: Male rats (Sprague Dawley, 8 weeks) were supplied with cinnamon in their diet (equivalent to ~1 g/day in humans) for two weeks. Blood glucose and lipid levels, as well as metabolic markers in both liver and abdominal white adipose tissue, were measured.
["<>Methods (Full Article Snippet): The study was approved by the Animal Ethics Committee of the Chengdu Dossy Experimental Animal Co., Ltd. (SCXK (Chuan) 2015-030). Sprague Dawley rats (male, 8 weeks, $n = 10$) were fed either standard rodent chow (14% fat) or rodent chow containing cinnamon powder (1 g/kg chow) for two weeks. Medical grade cinnamon (Sichuan New Lotus Chinese Medicine Pieces Co., Ltd.) for human use was added to the standard rodent chow by Chengdu Dossy Experimental Animal Co., Ltd."]
<>Results: Cinnamon significantly increased fat mass and blood cholesterol and low-density lipoprotein (LDL) levels but reduced fasting blood glucose level by 12%. Liver functional enzymes were normal in rats consuming cinnamon. However, several lipid metabolic markers were impaired which may contribute to dyslipidemia, including two main switches for energy metabolism (sirtuin 1 and peroxisome proliferator-activated

receptor-gamma coactivator-1α) and the LDL receptor. However, de novo lipid synthesis enzymes and inflammatory markers were also reduced in the liver by cinnamon treatment, which may potentially prevent the development of steatosis. Markers for lipid oxidation were downregulated in fat tissue in cinnamon-treated rats, contributing to increased fat accumulation.
<>Conclusion: Daily low-dose cinnamon supplementation seems to promote abdominal adipose tissue accumulation and disturb lipid homeostasis in healthy rats, raising the concerns regarding daily use in healthy people."[539.5.10]

Supplement & Prescription Drug Purity

Many supplements sold on the internet are laced with filler agents, especially bodybuilding and herbal supplements, which have "proprietary blends", which when translated to English often means "80% of the cheapest bulk chemicals, 20% of a potent

ergogenic chemical, and a sprinkle of fairy dust". Because of this it is far more intelligent to purchase singular chemicals, or extracts, that you can mix together to form your own proprietary blends, as these homemade supplement blends will be far more potent than that of junk supplement companies who use colorful, interesting, and *cool* advertising to condition us to conflate the art or advertising of a product for its efficacy and potency.

When buying purified chemical supplements always taste the product and compare that taste to other brands of the selfsame supplement, as many phytochemicals, ergogenic chemicals, vitamins, and minerals have a specific taste that you must memorize to increase your ability to verify the potency of the different products of different companies. You should taste every supplement you purchase, even if encapsulated, or in tablet form (use a pill crusher), as you will assuredly find that the potency of certain supplement brands is higher than others through what I call *oral reductive reasoning*. Filler chemicals are often added to supplements, such as sunflower lecithin, or dextrin, which each have their own characteristic taste, you should therefore always try to find pure supplements, even if you have to pay more, because filler chemicals do not only serve the role of enhancing the appearance of supplements or drugs, but of preventing their absorption in the gastrointestinal tract, which becomes a far more serious issue when considering prescription drugs which contain chemicals such as magnesium stearate, lactose, and cellulose, causing them to have bloated physical forms due to these filler ingredients. If you are able to compare prescription capsule or tablet brands, you need not taste the different varieties, just avoid the companies that produce the most bloated versions.

The Obesity Problem

The amount of effort that is required to become lean, when starting from an obese baseline, when a person has not mastered the sciences of macronutrients, or exercise, is remarkably high, and if hormonal issues are present, stimulating lipolysis becomes even harder.

It is my opinion, having suffered from obesity since late childhood, that the most effective route to lipolytic success is to embrace Endurance Training, performing over seven hours of low-moderate intensity cardiovascular exercise per week at the minimum. I see no reason why an obese person should focus on myogenic and aesthetic exercise (strength training) when only high volume exercise accelerates metabolism to a *statistically significant degree*. Resistance training with high loads to "burn fat" is not only dumb, but it is lazy, for anyone any learn to strain for a short period of time, but it takes strong resolve to learn to strain for hours at a time, or under the duress of the fires of Lactic acid. Aerobic / Cardiovascular exercises also serve the role of promoting cognition (inhibitory control / neurogenesis), and this is very important for those who suffer from overeating, or who are negatively influenced by the dietary choices and health nihilism of their friends or family members. If your spouse, family, or friends,

sabotage your weight loss journey, whether you are a fitness athlete or morbidly obese individual, you should obviously excommunicate them from your life until you reach your goals, for they do not respect you. But if separation is not an option, then enhancing your inhibitory control will be, and this will only occur through frequent cardiovascular exercise.

Regarding weight loss sciences, there is an unspoken problem of ***Lipolytic Lag*** as I call it, this encompasses the terribly slow process of lipolysis. We all know patience is required to burn large amounts of fat through diet and exercise protocols, but many people do not understand the sheer magnitude of exercise that must be performed and the severity of dietary restriction required to accelerate lipolysis to a degree that is noticeable and trackable each week. It is easier for a fitness-inclined individual to enter into a state of accelerated lipolysis because they are already physically active, and exercise is a passion for them, but for the average person, there may be far less time in the day to exercise, or outright incentive. In the absence of Endurance Training, one must be prepared for Lipolytic Lag, and expect to remain on a strict diet for many years before reaching their goals.

As I covered earlier, it offends me greatly to hear Podcasters & YouTube fitness personalities oversimplify fat loss as being merely changes to “diet and exercise”. If an obese individual suffers from recurrent psychological stress, dysbiosis, muscle weakness, high levels of intramuscular fat, negative food social conditioning, or hormonal issues, the Lipolytic Lag of their weight loss journey will be far more severe than what would be predicted. It is laughable that super lean individuals who use steroids, and potentially growth hormone, or clenbuterol, would even attempt to offer advice on lipolysis to someone at a severe myogenic and lipolytic disadvantage, or worse, criticize those who are too physiologically or psychologically unwell to elicit positive dietary change in their life. If my mother has taught me one thing on this planet it is that empathy and sympathy are the sharpest weapons of change, and to promote the adipocentric rehabilitation of those who have become slave to processed food and drink requires more than derision.

Finally, it must be mentioned that nutrient deficiencies play a major role in obesity and overeating, such that if you were to provide a multitude of vitamins and essential fatty acids to an obese man or women, not only would their metabolic rate increase, but so too would their ability to think intelligently about their dietary choices be strengthened, as a dysfunctional brain is more liable to make frequent errors. Ensure therefore, if you or a loved one is obese and a bad eater, that they / you never neglect the daily supplementation of a B-Complex high in thiamine, and the four essential fats, Linoleic acid, Alpha-linolenic acid, Docosahexaenoic acid, and Eicosapentaenoic acid.

The Cancer of Cleanliness

Axillary lymph nodes lie under the armpits, they filter pathogens such as bacteria and viruses, and most importantly cancer cells from the arm and chest. If these lymph nodes are damaged or disrupted through chemical toxicity, a person's chances of developing cancer increases drastically. Do you know where I am going with this essay? Think for a moment about the only chemical that is applied to our armpits on a daily basis. Aluminum-based Deodorant use is commonplace in nearly every civilized society, and it can be said that the greatest abusers of deodorants are women. Around 13% of all women in the USA develop breast cancer in their lifetime, that's about 260,000 cases of cancer development per year, leading ultimately to at or above 42,000 deaths.

Without citing research, because it is so very obvious, the high incidence of breast cancer in women, aside from being caused by phthalates, and other estrogenic environmental toxins, is clearly due to aluminum-based deodorant use, considering heavy metals such as aluminum accumulate in the skin, and a small concentration of their respective ions pass through the sweat glands and hair follicles, it must be possible that over a period of many years, the accumulating topically applied aluminum reaches the Axillary lymph nodes, to damage or disrupt them, leading to immunological failure—that being the failure to destroy cancer cells.

I do understand that natural deodorant sticks are highly ineffective, but there are few different innovative ways to prevent or halt epidermal microbial growth, such as the use of TALM's, changing ones diet, or altering ones stress hormone levels.

If it's not clear to you by this point, you should avoid the use of just about all OTC products for they are *poisons of convenience* and only serve the role of expediting our inevitable path towards death, similarly to junk foods. We have to wonder why so many products sold over-the-counter to treat symptoms, or make us smell pleasant, or maintain other forms of cleanliness, are so toxic, is it really just biomedical ignorance on the part of the manufacturers, or is there more to the story? When exactly does continued coincidence become a sign of intent?

Strength without Results

One should understand by now that training with high loads is not the most anabolic, or shall we say, myogenic method to grow maximal amounts of muscle tissue, nor is it sustainable over long periods of time.

It is my opinion that strength training or powerlifting should always be combined with the excessive dietary intake of protein and myogenic fatty acids, including the use of anabolic modalities such as Hyperthermia therapy, for what benefit is there is resistance training with high loads without the supplemental or therapeutic magnification of mTOR

or IL-6? Many gymgoers conflate neuromuscular junction adaptations with myogenic adaptations, they assume that because they are growing stronger or more powerful they are growing more muscle tissue, and sometimes this is true, but not always, as overtraining with high loads is a rampant issue in the fitness community, individuals who are addicted to lifting heavy weights are lulled into a sense of confidence, thinking every workout they complete is beneficial, even if they gain no muscle mass, but I consider this an error in judgement. For non-athletes, especially natural, it makes the most sense to me to confine high load training to brief periods in the year, periods where they invest the most time and money into anabolic supplements, food, and therapies, for why should they cause such drastic muscle breakdown in a physiological state of anabolic inferiority. We don't live in a world of dreams, if you are obsessed with exercise, and are to train a muscle group as often as you'd like, at the intensity you'd prefer, overtraining will invariably result, and you will never reach your potential.

Why are so many personal trainers obsessed with strength training their subjects when high volume, low load training is ideal for ensuring maintainable physical progression? It is not only a misguided belief that "big weights are required to build muscle", but also because *it is easier to strain, then to maintain (contractions)*, as anyone can be taught to exert near-maximal force, even if they fail during some part the range of motion of an exercise, while teaching someone to maintain tension on a muscle over the course of dozens of repetitions, while maintaining proper form, and not giving up due to lactic acid pain or fatigue, is after all far more difficult.

Lifting heavy weights in the absence of dietary protein, supplementation, and modalities is not only ineffective, but also a waste of life. Even if the neuromuscular junctions adapt, and strength increases, myogenesis will be perturbed, and physical longevity will only increase to a small extent. Considering the existence of myonuclei, and motor memory, there is no reason to attempt to grow stronger or more powerful every workout, unless this is your ultimate passion, in which case you are sacrificing your potential to accrue neurons and longevity-inducing muscle conditioning (angiogenic, glycolytic, whole-body lactic acid saturation) for far more ephemeral increases in muscle performance, which is fine if you plan your workouts intelligently, and utilize ARCS, but for the normal man or woman, I ask you this, why not lift light to live longer?

Exercise Order: The IL-6 Basis

Clearly the exercises you choose to train earliest in your resistance training workout will be the exercises that you excel the fastest at mastering, and this is because of the level of dopamine in the brain, as fatigue will always determine our ability, or willingness to maintain tension, and optimal form, of a specific exercise. But beyond neurochemical levels there is far more complexity to exercise order in its relationship to myogenesis. Firstly, when taking into account thermal therapies, especially Hyperthermia Therapy, the

muscles you trained last in a workout will always experience the greatest benefit from your post-exercise Sauna or Steam bathing if your workouts are hours long, such that if you train your upper body muscles over the course of three or four hours, and the last exercise in your workout is biceps curls, followed by an immediate steam sauna, the damage to IL-6 ratio of your biceps will be higher than that of your other muscles, or an another example would be if you completed a two hour upper body workout, which began with pressing, and ended with rowing exercises, followed by the use of a post-workout steam sauna, the muscles trained during your rowing exercises would have a greater time exposure of an anabolic stimulus (IL-6) than that of your pressing muscles. Now if you were to consume large amounts of L-Glutamine Pre/Intra/Post-Workout, then the hyperthermic IL-6 boost and effect of time might be overcome, but in most situations, Exercise Order will play a small role in myogenic propensity. The ideal way to overcome thermal therapy myogenic is to use circuit training, so that no singular targeted muscle group loses blood flow over the course of hours of training.

If supplements and modalities are eliminated from the equation, then training a muscle group or specific muscle pair that you wish to grow in size, strength, or power, earliest in the workout, is of course the most effective training tactic to use to achieve results, but when considering Hyperthermia Therapy, what you train last will always grow to the greatest extent. It is true that one could engage in Hyperthermia Therapy before a workout, but this is illogical considering that to optimally change our core body temperature is an uncomfortable experience, and is to be considered another form of exercise—the exercise of mental heat tolerance, therefore to pre-exhaust oneself with heat before an intense workout does not make sense, nor does it make sense to stimulate inflammation in the muscles before damage has occurred. I do understand that one may reply that to maintain an optimally elevated IL-6 expression in skeletal muscle, we could have two sauna sessions per day, pre-workout, and post-workout, but this is truly unsustainable considering firstly that the elevation in ROS would be highly damaging to the brain, and secondly that the amount of electrolytes lost each day would be difficult to recover through supplementation.

Optimal Glycogen Depletion & Replenishment

Part One

If we understand firstly that under normal circumstances, the human body will not enter into ketosis if blood glucose levels are high, and we understand that glycogen depletion accelerates the bodies entrance into ketosis, especially the depletion of liver glycogen then we can learn to master the sciences of the ketogenic state.

It seems logical to me to suggest that liver glycogen is not the only driver of the bodies accelerated entry in ketogenesis, or lipolysis in general, as our muscle tissue stores large

amounts of glycogen also. It may be wise then to train the entire body, with numerous compound exercises, low loads, and high volume on a high frequency basis during fasting or a ketogenic diet, to accelerate the bodies entry into a favorably strong form of ketosis. If the muscles are not depleted of their stored glycogen, blood glucose levels may fluctuate, thus perturbing the body's natural response to hypoglycemia; The Counter-regulatory Hormone Response, and eventual ketone production.

It is often said that full body training accelerates metabolism, but this is a meager oversimplification, for it is actually glycogen depleting high volume exercise that accelerates metabolism, beyond the transient increases in resting metabolic rate which occur post-strength training. This is primarily related to liver glycogen, which acts as a signal to the rest of the body to begin ramping up our primary alternative and adaptive fuel breakdown process (lipolysis).

In a perfect scenario, hypothetically, if one was to engage in upper and lower body endurance training, until experiencing near-complete glycogen exhaustion in the major muscles of the upper *and* lower body muscles, and if they were on a prolonged fast or on a ketogenic diet in the following days, I am almost certain that both lipolysis and ketogenesis would reach their peak far sooner than the average trends, which of course depend on activity level, diet, anti-diet, or exercise type preference.

Part Two

Many assume that post-exercise Glycogen Replenishment (Repletion) requires two or three days to complete, but in reality Glycogen Repletion is a rapid process that can take as little as 24 hours, if the meals following exercise are sufficiently high carbohydrate, ideally between 7-10g / kg for cardio athletes focused on performance and anabolism:

"<>Daily muscle glycogen recovery after training is important for athletes. Few studies have reported a continuous change in muscle glycogen for 24 h. We aimed to investigate the changes in carbohydrate intake amount on muscle glycogen recovery for 24 h after exercise using 13C-magnetic resonance spectroscopy (13C-MRS).

<>In this randomized crossover study, eight male participants underwent prolonged high-intensity exercise, and then consumed one of the three carbohydrate meals (5 g/kg body mass (BM)/d, 7 g/kg BM/d, or 10 g/kg BM/d). Glycogen content of thigh muscle was measured using 13C-MRS before, immediately after, and 4 h, 12 h and 24 h after exercise.

<>Muscle glycogen concentration decreased to 29.9 ± 15.9% by exercise. Muscle glycogen recovery 4–12 h after exercise for the 5 g/kg group was significantly lower compared to those for 7 g/kg and 10 g/kg groups ($p < 0.05$).

<>Muscle glycogen concentration after 24 h recovered to the pre-exercise levels for 7 g/kg and 10 g/kg groups; however, there was a significant difference for the 5 g/kg group ($p < 0.05$).

<>These results suggest that carbohydrate intake of 5 g/kg BM/d is insufficient for Japanese athletes to recover muscle glycogen stores 24 h after completing a long-term high-intensity exercise."[539.6A]

Note: I say cardio athletes because classical forms of low repetition bodybuilding or powerlifting training absolutely does not burn through large amounts of liver or muscle glycogen, unless someone possesses supraphysiological amounts of muscle tissue and is able to overtrain in the gym on a frequent basis owning to anabolic steroid use, there's no point in overconsuming carbohydrates if the majority of your workouts revolve around higher load-low volume resistance training. For the sake of unrestricted anabolism, physical training that is designed to prevent Glycogen Depletion, such as through Strength-Powertraining, is effective at giving the muscle tissue, especially the fast twitch muscle fibers, the stimulus they need to grow and thrive, but it is far from healthy, for not only the heart, or brain, but the muscles, it is a mistake for these muscles to not be given pause to initiate the processes of autophagy periodically, which of course is directly related to Glycogen stores, as an influx of energy or greater energy stores within or near a cell will always slow, or inhibit autophagic processes due to the promotion of anabolic signaling. Now how often should Glycogen be depleted, and the muscles allowed an *AMPK-Autophagic flush*, through changes to diet and a switch to high volume training? I surely don't know, you'll have to experiment for yourself, although I believe my Angio-Fast protocols come close to answering this question. In what regards Endurance athletes, this essays overreaching point is useless, considering they don't have to worry about the dangers of insufficient or inactive muscle autophagy, at least not for their cardio-trained muscles, their brains, and their hearts.

"Mass Gainers"

If gaining weight (fat + muscle) is a goal of yours because you are relatively lean, or skinny, consuming fast digesting carbohydrates in the form of "mass gainer" shakes will only make you ill due to hyperglycemia. Why would you consider it a good idea to spike blood sugar levels and promote aging processes when you could merely eat more slow digesting carbohydrates throughout the day, to utilize insulins adipogenic effects in a safer manner, by way of increased frequency of insulin release over extreme and transient surges? To gain fat safely, aside from steadily increasing the total carbohydrate concentration of each meal, and the frequency of meals, it is an excellent idea to increase your intake of essential fatty acids, especially Linoleic acid, which similarly to carbohydrates, is adipogenic in large concentrations, but being an essential component of the diet is far safer when overconsumed for the heart, brain, and muscles. As I have covered previously, many fitness influencers speak of the beneficial effects of accumulating intra-muscular fat, due to promoting muscle aesthetics, or some other

nonsense, and aside from this *superficial* argument, biochemically speaking, I disagree with this positive view of IM fat entirely, as the resultant blunting of insulin sensitivity and myogenic signaling that associates with intramuscular fat accumulation is almost never a good thing, and because of this you should be cautious that the "mass" you eventually put on is *clean*, meaning evenly split between muscle and fat, and not simply intramuscular fat, accompanied by insulin resistance, and a trend towards developing hyperglycemia due to the excessive consumption of Oleic acid, Palmitic acid, & Fructose, which will damage the body in exchange for rapid adipogenesis.

Finally, remember that chronically elevated inflammation destroys adipocytes, and if you have supreme difficulty adding body fat to your frame, you might want to consider experimenting with large daily dosages of Ascorbic Acid and Tocopherols to slow metabolism, and quell excess inflammation, to thereby promote adipogenesis. If this fails, and all that results from increasing your macronutrient intake is the development of illnesses, then there is always the future therapy; Carbon Dioxide Bathing.

Hypertrophy ≠ Intelligence

I have learned many things from popular bodybuilders, and powerlifters, especially regarding optimal exercise form, but as I have grown older I have begun to lose my respect for these people, not because they are of inherently bad character, or necessarily egotistical, but because they have forgotten, or fail to understand the difference between enhanced and natural lifters. I no longer seek wisdom or knowledge from those who use steroids because *they are not us*, and I say that not from a spiteful or jealous place, but instead from basic logical analysis and experience. I could name dozens of fitness influencers, but I will refrain from doing so, because you already know who they are by a quick glance of their physiques or their suspiciously high level of strength, or power. The way that they train is not applicable or appropriate for a natural lifter, and yet they train other people with their own bodies as inspiration, as covered previously, ultimately causing injuries, or myogenic plateaus.

If you follow any of the major fitness communities, you'll notice that the amount of young men and women with supremely impressive and muscular physiques, including those who are super lean, and those with exceptional muscle power, has climbed drastically in the last decade, and this is not due to the evolution of training methodologies, it's simply the result of a greater access to numerous different anabolic steroids, including the highly lipolytic compound growth hormone. This blatant fact has made me hyperaware of the superficial and vapid nature of fitness personalities, those who cling to their drugs so tightly as to not lose followers, subscribers, or clients due to the loss of skeletal muscle, muscle strength, or power. Many of these people are very insecure individuals in the end and in need of serious psychotherapy. I surely understand

there exists super intelligent, and thoughtful people who populate the fitness social sphere, but they are few and far between.
At this point in my life, I am far more inclined to listen closely to the training ideas and experiences of a natural athlete, or a random passerby, a person who must conquer injury, and fight off muscle atrophy with a *much greater amount of forethought*, even if they have unimpressive bodies. And I tend to purposefully ignore, as you should learn to do, detailed training advice, beyond advice on exercise form, from those who have a far greater ability to heal from wounds (muscle injury).

Humorously, steroid users will suggest that to reach peak physicality requires "training hard", and maintaining a "perfect diet", not "just drugs", but these aren't difficulties or obstacles in the life of a bodybuilder, powerlifter, or athlete, natural or not, they are instead the intense protocols and rituals (Sublimation-Obsessions) fitness-inclined minds love, therefore, this is merely a rationalization and ill-conceived retort from predominately bodybuilders and powerlifters, it is their favored platitude to brush away the criticism that their potential wasn't reached because of hard work, but because of the use of difficult to acquire and extremely potent synthetic drugs, which in reality is not an insult if the playing field is level and if they are in active competition with other anabolic steroid users. Strangely, even with the neurotrophic effects of Testosterone—that of which is considered the essential starter and base anabolic steroid on every serious competitive bodybuilding and powerlifter drug protocol, most steroid users are intellectually impoverished (vapid), and this is proof that without psychological conditioning (engaging in cognitive challenges; learning), enhancing neuronal growth is relatively fruitless for the promotion of complex intelligence.

I would ask that you show me or tell me what you accomplished as a natural athlete, however meager it may seem, from burning twenty pounds of fat, to increasing your bench press 1RM by ten pounds, and in doing so I will give you my total respect, but if you merely flex your unnaturally large muscles, or pick up a giant amount of weight (leaving aside natural power), I will turn away from you, because we exist in a different world of training and supplementation, and you have already lost a large amount of my respect, because I assume, possibly unjustly, but often correctly, that you don't remember the extremely complex difficulties of training unenhanced, and the confidence and motor memory skills you display in the gym are dependent not on sheer willpower, but the luck of finding and maintaining a trusted drug dealer. When or if steroids (leaving aside TRT) ever become legalized, this will no longer be an issue, but for the present time it is important to choose your role models carefully, as anyone can grow impressively large, lean, or strong with the use of steroids, combined with a high protein diet, intense training, and a moderate level of mind-muscle connection, but only the most determined natural athletes can accomplish these aspects of physical change through intelligent programming, and painful trial and error. Even in the cases where individuals use steroids, and do not grow a tremendous amount of muscle mass, neither do they become supremely strong or powerful, either because of insufficient diet, overtraining, or weak

motor IQ, they are still able to train harder, longer, and more frequently in the gym, leading to a far greater post-exercise boost to lipolysis, therefore it is not a logical retort to my criticism to suggest that "steroids don't build muscle if you don't know how to train, or if you do not train hard enough".

Learning from professional powerlifters how to move the body for maximal force distribution between large muscle groups during compound lifts is beneficial, and watching the training videos of popular bodybuilders to learn what exercises they perform to inspire variation in our own training is also beneficial, but attempting to mimic their own specific workout protocols, or follow their personally programmed (*anabolically biased*) training programs made for you, or attempt to mimic the exact results of their training fundamentals, is both illogical and dangerous for your body. Similarly to the Halo Effect of psychological bias, do not fall prey to the *Titan Effect*.

The Ego Crucible

In the event that a muscle, or group of muscles do not want to grow, either because of injuries, or years of high load overtraining, such as demonstrated in the tiny but super dense and powerful biceps of powerlifters, and even many average gymgoers, the last remaining option aside from anabolic steroids, or the experimental use of controlled research chemicals, is low load training, including first and foremost, Occlusion Training, followed by LAT, and finally simple and super light weight Aerobic Training. To hypertrophy a highly damaged, or deformed muscle will require hundreds of hours of carefully planned, low load training sessions. You can't complain about having a lagging muscle group when you aren't willing to rehabilitate it properly, through high frequency and high volume angiogenic training. Of course, there is no doubt the very best training method for promoting hypertrophy and reactive angiogenesis is Occlusion Training, but considering Aerobic Training (1-3% 1RM) results in such little damage to muscles, and is also highly angiogenic, there is no reason not to engage in Hike & Curl, or even Curling while on a recumbent bicycle, or treadmill, every day. And Lactic Acid Training, being the most technically demanding, should be performed the least often, due to the neurological demand it requires. The general idea is that if you train a weak, injured, or deformed muscle group with weights between 1-15% it's 1RM, (ideally 1-7% 1RM), and perform hundreds of thousands of repetitions per with these low loads, while feeding your regenerating muscles with amino acids, carbohydrates, and fatty acids, there is no possible way you won't see major hypertrophic changes in this specific muscle pair, or group.

Regarding the Biceps, luckily they are the easiest muscles to rehab & train through aerobics, because we can curl while we walk, or while we are cycling, thus combing cardio with arm training, but other muscles will require more technically demanding body positions, and therefore they will require a greater time sacrifice, but if

hypertrophying a certain muscle group is your ultimate goal, you should not find the inconvenience of lost time, or the potential embarrassment of lifting super light weights in the gym as a significant detriment to your progress. If you can maintain consistent training, and steer clear of Ego Lifting, you will find that these low loads bring you safely, slowly, and predictably to the development of large muscles.
Finally, remember we are discussing low load lifting for the promotion of not only safe and subtle hypertrophy, but more precisely angiogenesis. If you intend on maintaining an Anti-Cycle (Anti-Angiogenic Cycle) for extended periods of time, your best option is low load training combined with extended detraining periods, such as 96 hours or greater, ensuring that each workout you perform is sufficiently intense, but not overtly damaging the muscles in question, and taking very large amounts of Quercetin to facilitate delayed, but significantly enhanced hypertrophy. Also, regarding "Aerobics", you should absolutely never surpass 3% your 1RM, no matter how strong, or healthy your muscles feel, for you must remember that the mind is not equal to the body, which is how you likely ended up with inefficiently hypertrophied, or chronically overtrained muscles in the first place. The ultimate goal of muscle hypertrophy is growth, not destruction, and people are only beginning to understand this vitally important physiological concept, whereas the ultimate goal of muscle conditioning is neuromuscular junction adaptation, which often requires sacrificing muscle tissue through overtraining to facilitate NMJ function.

Tea, Unpleasant Flavor Sensations, Energy Drinks, and Sweeteners

Part One

It is sad that the tea community is filled with supposed experts that promote relatively short brewing times for high end teas, to create "*subtle*" and "*pleasant*" flavors, and tactile sensations (Astringency, Pungency: Mouthfeel). This is of course directly counterintuitive and a distraction to the primary purpose of liquid phytochemical extracts, as unless the goal is microdosing phytochemicals or caffeine, Tea should have a relatively strong flavor, unpleasant many would say, as this ensures that the concentration of phytochemicals within the brew are adequately dense for the promotion of health. It is entirely possible to recondition yourself (psychologically) to learn to attribute powerful flavor or tactile mouth sensations such as astringency, sourness, or bitterness, to good outcomes, which will result in the easier adherence to a supplement protocol that involves the consumption of liquid or powder herbal extracts or bulk ergogenics, including medicinal mushroom powders, which as aforementioned should have a very unpleasant flavor when consumed in liquid form, such as when blended, or added to a shaker cup. The more you force yourself to consume drinks or foods with unpleasant oral sensory sensations due to phytochemical or mycochemical supplements, extracts, or powders, the

healthier you will be in time due to the increasing ease and reconditioning-induced taste desensitization. Attempting to confine all of your supplementation to Oral Solid Dosage Forms is lazy, and not ideal for the promotion of health and general wellness, as there are many herbs, fungi, and laboratory synthesized ergogenic chemicals that will exert no noticeable beneficial physiological effects when consumed in milligram dosages. If you always rely on sweetness and fatty acids to subdue antioxidant flavor sensations, your progress towards optimal health will be hampered. Think of how prevalent artificially oversweetened protein powders are in the market, is that daily dosing of sucralose really doing anything for the body except for conditioning the brain to associate exercise with sweet flavors?

Regarding the natural caffeine sources people choose, such as coffee, although it may be assumed that the consumption of moderate amounts of coffee will elicit quite similar effects on the brain and body as the moderate consumption of tea, because people often hear it reported that coffee is rich in antioxidants, this is simply not true, as the mental stimulation achieved from coffee is vastly different than from tea (green, white, and black). Considering that coffee, owing to its far weaker antioxidant profile, is liable to increase IL-6, and Caspase-3, and potentially certain ROS to a greater degree than Camellia Sinensis teas, the mind and body effects of coffee versus tea will always be different. I believe that consuming large amounts of coffee is far more likely to cause limbic system dysfunction, impulsivity, hysteria, and moodiness, whereas black tea has the reverse effect, and green tea only relates to moodiness through a potential dopamine disturbance. If someone is about to engage in high intensity destructive training on a conditioning protocol (high volume), consuming large amounts of coffee (or simply using inexpensive caffeine pills) makes perfect sense, as it will invariably promote two very specific forms of inflammation in the body, unfortunately it makes absolutely zero sense to consume coffee every morning out of habit alone, or before low intensity workouts, or worst of all, while sedentary, when one could be consuming antioxidant rich green tea, or the slightly weaker white and black teas, thereby delaying their physiological decay. Refer to the list below for my ideal use of Natural Caffeinate sources:

- Coffee (Caffeine Powders / Pills): Overtraining (Max Load Lifting, Intense Endurance Exercise, High Frequency Exercise).
- Camellia Sinensis Tea: Optimal Training (Moderate Load / Moderate Intensity Exercise, Optimal Detraining).
- Uncaffeinated Tea: Detraining / Undertraining (Low Intensity Exercise).

As a bonus here is my chemical-sensory hypothesis for the reason behind Astringent tactile sensations: Green Tea catechins have an Astringent and relatively unpleasant taste profile due in my hypothesis to the potent antibacterial effects of the aforementioned chemicals. I discovered the idea for this hypothesis when in my teenage years, being

unable or unwilling to swallow pills or capsules, I ground up an antibiotic that was prescribed to me and drank it, which I will say was one of the most unpleasant sensory experiences I have ever encountered, and during my forced examination of the aftertaste of this drink I noticed that the tactile sensation was extremely Astringent, precisely like my experience with brewing and consuming extremely strong generic green tea in its purest form, without sweeteners, or cream. In my view, when the microbiota that populate our tongues are damaged, they release endotoxins, which results in an Astringent tactile mouth sensation. Therefore, in this view, Astringency is merely the *taste bud microbiota-endotoxin mouthfeel response to chemical antimicrobials*.

Part Two

Energy Drinks are ubiquitous in developed nations, and commonly abused by young adults, who are addicted to the oversweet flavors, and carbonation. I wish people understood that the ingredients added to Energy Drinks cost so little to large companies during manufacturing, less than 3-5 cents per 200-300mg caffeine, or 4-8 cents for B-Vitamins, that what they actually pay for when they buy an Energy Drink is not the chemicals therein, but moreso the advertising of the product. When you purchase a bottle of Kombucha you're getting two things in return that are difficult to produce at home, those being a low dose alcohol drink, and a carefully maintained probiotic extract, whereas because caffeine and B-Vitamin supplements can be found at every store, for far less cost, it is monetarily unwise to waste money on Energy Drinks. These large Energy Drink companies aren't successful because people on road trips, or doing overtime, need a quick and easy boost in energy, they're popular because of the toxically high level of artificial or natural sweeteners added to each drink, which attract young people, who end up developing dysbiosis, and altered dopaminergic signaling in their brains. There's nothing wrong with consuming a banana blueberry smoothie, or glucose drink during or post-exercise, especially for glycogen-depleting exercise, and neither is there error in adding sugar to a caffeinated beverage to prevent blood sugar drops, but why should we support Energy Drink companies that utilize extremely inexpensive chemical components, who use targeted advertising and branding, bright and colorful, to attract the attention of teenagers, and even children? Until the point in time that Energy Drinks begin adding chemical components that are truly impressive, not just mass produced and cheaply synthesized B-Vitamins, or microdosages of phytochemicals, there is absolutely no point in purchasing their trash products. Also, do understand that with the advent of home soda making machines, we can make our own Energy Drinks, and add novel and experimental ingredients, such as amino acids, or other ergogenic chemicals, depending of course on solubility. It is very possible to produce a similarly tasting and similarly physiologically-effecting Energy Drink at home, as in the stores, for a quarter of the cost, or less.

In terms of workout glucose powders, if premade carbohydrate drinks are a necessity for you, why not purchase some V8 or off-brand Vegetable Juice to sip intra / post-workout? At least these vegetable carbohydrates suspended in a liquid solution are adjacent to antioxidant nutrients, and nitrates, which will make you feel far better physiological post-workout than if you were to consume some inexpensively produced dextrose-based "Carbo" powder.

I must now speak about Protein Powders, and Pre-Workout Powders, as they too are oversweetened by natural and artificial sweeteners. Why does every drink that you consume have to taste like a candy bar? Is that not immature, but more importantly, is that not unhealthy? Because at the time of publishing book, the majority of popular protein powders and pre-workouts powders are sweetened with Sucralose, which as we have learned spikes insulin, NPY, and promotes the growth of Ecoli in the gastrointestinal tract, I would suggest you go the unflavored route for supplement powders if you wish to remain healthy. Also, why even consume powders sweetened with phytochemical sweeteners such as Mogrosides, if you don't suffer from diabetes and have uncontrollable sweet cravings? It's quite strange to stimulate the release of Insulin, while not consuming adequate amounts of carbohydrates, for it makes no sense to increase the bodies glucose utilization rate without adequate blood glucose in place. One should give up all sweeteners, even sweet tasting amino acids, if they wish to burn large amounts of fat as Insulin is the primary enemy of lipolysis, not blood glucose, although they coincide more often than not, low calorie sweeteners and amino acids prove that these two cascading processes can be separated.

It is extremely common for older women to sip on sugar-free natural or artificially sweetened drinks, assuming they are being healthy, while also complaining about being obese, or remarking that they have no energy exercise, while they skip protein meals. These women stimulate insulin release to great extents while depriving their sensitive bodies of amino acids and fatty acids, which I know only accelerates their aging processes. It is better to be obese in old age with a good amount of skeletal muscle, than to be addicted to sweeteners, natural or not, and their insulinemic effects, and also obese, but physically undeveloped and atrophied.

Microbiome Mastery

Remember when I said that longevity can be attained even without the severe restriction of dietary carbohydrates? I believe that with the pricey use of homemade, home brewed, and store bought probiotics, a human being can delay aging significantly, primarily through reducing chronic forms of inflammation, delaying immunosenescence, and through providing the brain with the neurotransmitters it craves by way of symbiotically

produced extracellular vesicles, and there are obviously many more benefits that I am neglecting to mention.

This pathway to increased longevity is best suited to those who find the greatest comfort in a Pro-Inflammation Cycle, because probiotic use is a much more subtle way to change physiology and reduce inflammation as compared to phytochemical use, and because certain probiotics promote angiogenesis, therefore proving their benefit for the promotion of muscle and brain health.

The primary detriments to focusing solely on microbiome health are monetary cost and time consumption, where the former is a much greater obstacle to overcome if you use supplements, the latter will be a more complex difficulty for most people to overcome, for carrying for probiotic cultures and creating fermented foods and drinks will take culinary skills and a great level of patience.

It may be true that the only supplements a human requires to live a long life, while maintaining impressive amounts of muscle tissue, and cognitive function, is essential nutrients, with the addition of probiotics.

On the following page is an organized list of probiotic drinks, foods, and supplements that you can make at home or purchase at the store:

DRINKS:

- Amazake.
- Kefir (or Kefir Water).
- Kvass.
- Kombucha.

PROBIOTIC FOODS:

- Sauerkraut.
- South Korean Cultured Kimchi.
- Yogurt.
- Yakult (Lactobacillus paracasei)
- Cottage Cheese (Made with Lactobacilli).
- Raw Sourdough Bread (uncooked).
- Pickles Cultured with Lactobacillus Plantarum.
- Cultured Sour Cream.

PREBIOTIC FOODS:

- Chicken.

- Broccoli.
- Oatmeal.
- Rye Flour.

SUPPLEMENTS:

- Lactobacillus Plantarum
- Lactobacillus Rhamnosus.
- Lactobacillus Casei.
- Lactobacillus Reuteri.
- Lactobacillus Acidophilus.
- Lactobacillus Helveticus.
- Bifidobacterium Longum.
- Bifidobacterium Breve.
- Bifidobacterium Bifidum.
- Bifidobacterium Animalis.
- Bifidobacterium Infantis.
- Bacillus Coagulans.

In Place of the Ketogenic Diet & Anti-Diets

In certain scenarios where an individual cannot maintain a ketogenic diet, or engage in fasting, due in part to gastrointestinal motility issues, it is still possible to diet effectively and speedily to promote lipolysis, although the concurrent fat loss will almost never be equivalent, there are still other options to choose instead of the complete restriction of all dietary carbohydrates. The best idea I have found to overcome the issues of the Ketogenic Diet is through the Fermented Cabbage Diet, where you ensure that with each high protein meal you consume half a cup or more of Sauerkraut, or low sugar content Kimchi, to promote satiety, and gastrointestinal motility. Because cabbage is extremely low carbohydrate, and considering that most of its ascorbic acid and phytochemical content will have degraded during fermentation and processing, its anti-inflammatory, and thereby anti-lipolytic physiological effects will be far less than that of freshly prepared traditional greens loaded with vitamins and phytochemicals, making it an excellent food source to utilize during traditional, inflammation-based dieting. If the taste of fermented foods is too much for you to bear, you can also experiment with adding Nonfat Unsweetened Greek Yogurt to one of your meals per day (or more if you are not *regular*), 1/4th cup, equating to 4-7g of carbohydrates, as this should not perturb your metabolism greatly, but it should promote gastrointestinal activity due to the moderate concentration of lactose present therein. For the Emergency Lipolysis Protocol, or the ODDS Protocol, it will not make a drastic difference to change your diet to align with

super low carbohydrate eating, but it absolutely has to be super low carbohydrate foods only, this is of course to avoid insulin fluctuations.

The Fourth Compound Lift

Rowing is not often considered an important exercise, as compared to the Squat, Deadlift, & Bench Press, but the biceps, posterior deltoids, and upper back muscles play an integral role in facilitating all three previous exercises. Although there currently exists Curl Competitions, that is just not good enough, we must push for the parallel prone row to be considered the Fourth Compound Lift, so it can be including in Powerlifting competitions, and used to accrue new "totals", for why is pressing absolute strength more impressive than rowing absolute strength? It just does not make sense to me. Also, if powerlifters were to specialize in rowing too, they may be more likely to deload, or detrain their biceps properly, instead of overtraining them so harshly every week.

Now whether my dream comes true or not is irrelevant, as rowing exercises should not only be considered "accessory movements", as this will create an imbalance in the body over time, and cause numerous injuries. Even if the biceps do not become overtly injured due to high frequency, high load back training, coupled with isolation arm training, it is still wise to give them respite at times from the catabolic onslaught of training you most likely put them under each workout. Those who have found the greatest success from training their arms multiple times per week, through back training, and isolation arm training, with heavy weights, are nearly always steroid users, and you must remember that you are not who you aspire to be, your unremitted willpower is not enough to bring you to their physiological state.

As for my hypothetical rules of a Prone Row Powerlift:

1. Clearly it will need to be performed on a tall prone row exercise apparatus, allowing a person to reach a level torso position when laying on their stomach, as opposed to the use of an improvised incline bench.
2. There would be a rule to disqualify anyone whose upper or middle pectorals lose contact with the bench pad, to prevent arching during the rowing ROM (not including unracking), to prevent someone from cheating through contracting their rhomboid-thoracic extension (arching their back), rather than solely using their arms and shoulders.
3. The movement will always start with the arms completely outstretched and loaded completely, and the weight will be held for 3-4 Seconds to prove the lifter is in control of the weight before initiating the movement.
4. There will be no need of spotters, as the weight can be simply dropped if failure in the lift occurs.

Antiquated Caloric Restriction, Drugs, & Inflammation

If you intend on using chronic amounts of Nicotine, or another inflammatory chemical, on a Pro-Cycle, it is important that you do not imbibe on macronutrient dense meals without chronic cardiovascular exercise (120mins / day) as the overconsumption of carbohydrates and fatty acids will only exacerbate the neurotoxicity of inflammatory compounds. Reducing your daily consumption of carbs, fats, and even protein while under the influence of neurotoxic chemical compounds is not an unwise idea, if this change to diet is temporary, and used to further enhance angiogenesis, or lipolysis, but do understand that if you begin to plan your exercise types / techniques and diet around a drug, you know you're suffering from some form of subtle or chronic addiction, and you should eliminate it from your routine until your solve your life's issues. Similarly to those who say they adore the flavor of coffee, but never drink it without copious amounts of sweeteners and creamers, if you only workout when you have Pre-Workout powder, or an Energy Drink on hand, you need to reevaluate the actual pleasure, confidence, and contentment you attain from exercise. Although earlier I suggested drugs are best combined with exercise, this is not to create an interdependence, it is to reduce the total daily time of being "high", or in a *neurotoxic state*. Alas, even in scenarios wherein person will only choose to exercise while under the influence of a mind-altering substance—this is still a far better result than the other option—of getting high at home, sedentary, while zoning out to televised lies, and fictional dreamscapes.

Recreational drugs such as Caffeine, Nicotine, THC, and Alcohol, are merely psychogenic supplements of variable efficacy, although we don't think of them as such, they are *evolutionary tools* we were given to experiment with, often to our own detriment.

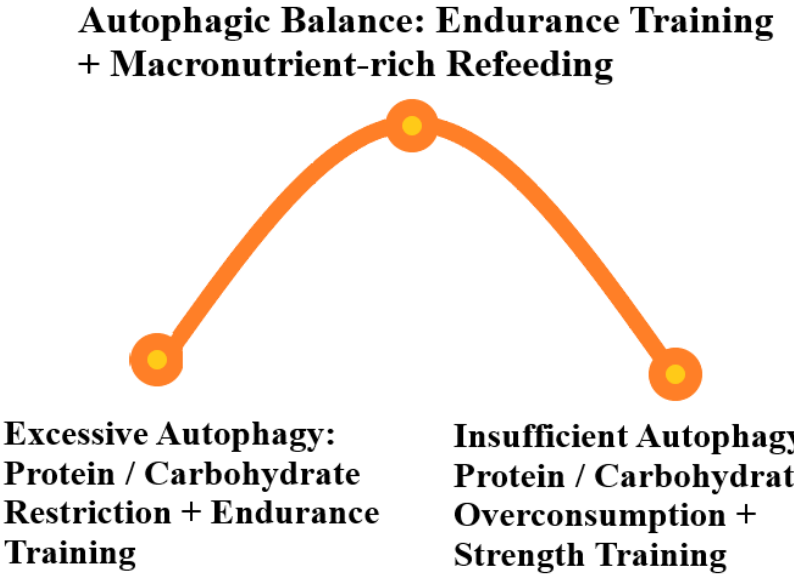
The Boogeymen of Longevity

Insulin, and by proxy mTOR, are not the inherent enemies to healthy aging, but they become such during periods of physical inactivity, or shall we say, *exercise volume insufficiency*. For those with exercise protocols that do not include intense, enduring, and frequent cardiovascular exercise, a diet super high in protein, and GlySer, will only age their bodies, but there is far more complexity to aging than simple biochemical measurements. To have muscle is far better than to not have muscle, and considering muscle mass is generally lost during aging, especially in natural gymgoers, I do consider it essential to incorporate strength training into your protocol during youth, but after you begin to decay biologically, beyond age forty, you should begin to specialize in cardiovascular exercise, and aerobic exercise, to ensure that your brain and heart are being oxygenated, and stimulated through lactic acid efflux.

Although the vast majority of Endurance athletes consume copious amounts of carbohydrates every day, they time their carbohydrate consumption to pre, intra, and post-workout. This means that they do not, on average, experience hyperglycemia, as the consumed energy is being utilized intra / post-exercise to fuel the muscles, to spare, and

to and replenish glycogen stores. In this respect, Endurance athletes truly have mastered the science of carbohydrate use, whereas bodybuilders, and powerlifters, and recreational strength athletes have not. There is no reason to consume large amounts of fast digesting carbohydrates (i.e. classic white rice bodybuilder diets) all day, every day, especially when glycogen-depleting exercise is not engaged in (Endurance Training), as this will only raise mTOR and blood glucose levels to unnecessarily high levels. There is no doubt in my mind that the pro-senescent effects of Insulin are at the least partially overcome through the generation of large amounts of lactic acid, making Insulin irrelevant towards longevity sciences in Endurance athletes. It can also be said, at a certain point when a person's body fat has reached its lowest point, that continued high volume training will only result in excessive proteolysis, as adipose tissue is no longer a fuel source, thus making carbohydrate consumption (or fatty acid consumption) essential for not only performance but also muscle health during aging in those who engage in dozens of hours of Endurance Training each week, and are of very low total body fat percentage.

As a final clarification, the previous information is based on natural athletes who specialize in strength training, not Endurance Training, and are not enhanced. An enhanced bodybuilder, or powerlifter, owing to a substantially increased total amount of lean mass, and far more intense resistance training sessions, will always be able to metabolize far more carbohydrates every meal than their unenhanced opposites. Consuming 300+ grams of carbohydrates per day through the intake of fast digesting white rice carbohydrates will do a natural athlete no favors in promoting muscle growth (leaving aside ARCS), unless they are mimicking their hypertrophied idols and consistently overtraining in the gym, in which case a severe injury will invariably occur, which will inevitably reduce their exercise sessions' intensity and volume, leading to accelerated cellular senescence due to the excessive intake of carbohydrates each day, and the resultant steady-state hyperglycemia, or hyperinsulinemia.


Autophagic Balance: Endurance Training + Macronutrient-rich Refeeding
Excessive Autophagy: Protein / Carbohydrate Restriction + Endurance Training
Insufficient Autophagy: Protein / Carbohydrate Overconsumption + Strength Training

Remember that autophagy is regulated by exercise, specifically cardiovascular exercise, and if performed at moderate intensities (viz-a-vi 70-75% Max HR in my estimation for the *optimal* & *sustainable* stimulation of systemic autophagy), and for Endurance Times (120-Minutes +), a post-exercise high carbohydrate / high non-essential fat meal such as Pizza will not promote aging, not to a noticeable extent. No doubt, if you only perform half an hour of Moderate Intensity Cardio, and eat junk food post-workout, you will become sickly over time, as only higher level Endurance Training of 120-Minutes or greater (in my opinion), will allow you the metabolic freedom to binge eat junk food post-workout without consequences. Although higher intensity cardiovascular exercise may promote greater autophagy, your chance of injury increases with each percentage point of your MHR you increase.

We all Starve Together

It is true that fasting, and maintaining a Ketogenic Diet will change the gut microbiome, most likely by reducing the density of Firmicutes bacteria, our favored family members. This may be beneficial for increasing systemic inflammation, to magnify the processes of myogenesis, or lipolysis, but in some cases wherein an individual already suffers from chronic levels of inflammation, from prescription or recreational drug use, or recurrent psychological stress, the reduction in Lactobacilli bacteria in the gastrointestinal tract will only exacerbate the neurotoxicity and synaptic dysfunction that results.

Now, it must also be mentioned that a diet of dysbiosis-facilitating carbohydrates or fatty acids, such as with processed foods, fructose, sugar, and the overconsumption of non-rye based grains is also liable to disturb, or facilitate an unhealthy microbiome signature. If you aren't going to eat vibrant red, green, yellow, and purple vegetables, those high in soluble fiber, and low in carbohydrates, and instead choose to eat sweets and grains, intermittent fasting, or the Ketogenic Diet may benefit you, even if the gut Lactobacillus strain density does not increase, due to the effect of starving bad bacteria, such as Ecoli, Clostridia, and Bacteroidetes. Although Bacteroidetes may increase during a fast, this is in my opinion due to refeeding choices, for it does not make microbiome-sense to refeed after any sort of fast, or Ketogenic Diet, with junk carbohydrates, and common grains, as many people do, especially Muslims during Ramadan (The future of Islam should surely involve Keto-Fasting during Ramadan), as this will only condition your brain in a negative way as to associate sweet or carb-rich food as a reward for voluntary macronutrient abstention and starvation, and it will condition your gut to grow the sort of microorganisms that will destroy you through physiological sickness in later life. Just because you "feel healthy" on a bad diet, doesn't mean you are healthy, as it's quite possible the Extracellular Vesicles that the toxic bacteria are producing in your gut are giving you a false top-end (neurological versus physiological) cellular optimism, a *neurotransmitter cargo gut-to-brain-induced overconfidence*. This dangerous neuro-cellular optimism is evidenced by that the fact that many of the individuals who have sudden heart attacks, or strokes, even during periods of outwardly superficially appearing good health, and inwardly feeling of good health, can have their life's cut short so fast, so

seemingly unpredictably, due to them conflating how they feel mentally to how they feel physiologically.

I understand that there is more complexity to human health than the microbiome, that there are numerous essential nutrients to consider, and other variables such as psychological stress level, environmental toxin exposure, sleep hygiene, and exercise intensity – volume – and type, but health most often begins from within, and when I say "within" I refer to the intestinal florae, for they are the master control units of our immune systems, and our brain health, and to ignore them is to doom yourself to a life of sickness and suffering.

To B, or Not to B, that is the Question

The use of Vitamin B12 is rampant, especially among young people, who falsely assume it to be a potent neuroprotectant, and nootropic, but they are confused, as only Thiamine is to be considered the strongest vitamin neuroprotectant, and essential nootropic, pretending for a moment that Ascorbic Acid does not exist. Thiamine promotes Glutamate uptake in the brain, thereby reducing the chances of excitotoxicity, whereas Cobalamin is an outright NMDAr antagonist, which will also protect neurons against excitotoxicity, but will also carry with it the side effect of reduced memory acquisition, consolidation, and retrieval, as our NMDAr's are so very important for cognition. The combination of unnaturally high concentrations of B12 and Caffeine only exacerbates the impulsivity and short term memory loss inherently displayed in energy product addicts, especially those who are young and sleep-deprived, who neither remember, nor are capable of remembering what they just said fifteen minutes ago to a coworker.

I will clarify that I see no reason not to use and abuse B-Vitamins, as they pose very little toxicity due to a high excretion rate, but for those who enjoy maintaining an optimal level of cognitive fitness, B12 use must be mitigated, to avoid supraphysiological concentrations accumulating in the brain, disrupting our fragile memory processing abilities.

THC, Motor Pattern Dysfunction, & Worker Drones

Part One

More often than not I can tell what drug a person uses by the motor coordination, motor fluidity, and motor speed of their bodily movements, movements which have a special signature to them that allows me a deeper insight into a person's recreational habits. Whereas Nicotine and Caffeine use are more difficult to distinguish, but are separatable by the speed of motor movements, the long term abuse of THC and it's resultant neurotoxicity is extremely easy to spot, not just through delayed speech, or an altered

blink rate, but through obvious motor movement stiffness, where those who have abused THC in youth for many years begin to move robotically when actuating old motor patterns, displaying obvious movement pattern rigidity, and this is an indication of motor memory dysfunction, explainable by disrupted dopaminergic-based basal ganglia synchrony, and GABAAr receptor underactivity. Reduced head movement, and neck stiffness are the primarily signs I look for in THC addicts.

For those who are young and combine chronic THC use with exercise, such as MMA sports, the locomotive symptoms is far less noticeable, due in part to the neurotrophic and neuroprotective effects of cardiovascular training, but for those who get high, time and time again, without counteracting their neuronal loss, neurotransmitter changes, and brain wave disruptions, they become human automatons, displaying unhealthy muscular rigidity, and severe behavioral inflexibility.

Part Two

The legalization of Marijuana, and THC derivatives, will undoubtedly result in the rapid decrease in IQ's across the lower income strata's of society, as these peoples indulge themselves in a dissociating escape from their more often than not difficult and monotonous jobs. I understand that many will argue that THC, similarly to Nicotine, or Alcohol, stimulates creativity, and this is true, but the creative results of THC abuse is simply not the same, as the greatest drug-enhanced works of literature and art were made while under the influence of Alcohol, and Nicotine (Pipe / Cigarette Smoking), because our analytical intelligence is not disrupted completely while under the heavy influence of the former drugs, and whereas THC is capable of promoting a COX-2-induced inflammatory-creative surge, this inflammation is far less sustainable for a human brain, regarding intelligence, as compared to the previous two options, as THC only promotes COX-2 expression in high concentrations, whereas Alcohol & Nicotine exert their potent mind-altering effects at any concentration administered. Also, bDNF expression experiences rapid changes following chronic Alcohol and Nicotine use, and their withdrawal, but THC use, owing to its fat solubility, is never truly withdrawn from in those who use it daily, weekly, or monthly, in high concentrations. These effects culminate in a steady decrease in intelligence, and more importantly a decrease in the ability to actualize comprehensible creativity—the forms of creativity that go beyond abstract art, brainrot (childish and schizophrenic TikTok humor), and other forms of incomprehensible and embarrassing human expression.

It is only a matter of time before the HR departments of megacorporations begin to understand the benefits of hiring Cannabis addicts, and promoting their addiction through company incentives, as a worker bee that loses its creative vision will never stray too far from the hive, ultimately become slave to the scents of predictability, which is the ultimate *corporatist opportunity to profit from behavioral inflexibility*.

We must remember that with the paired use of chronic THC and caffeine (which will only exacerbate the concurrent cognitive dysfunction), the ability for a human being to change the road they tread in life in the most logical way—to enhance their survivalism through intelligent divergent thinking, will be made tremendously more difficult, except for cases of blind luck (or divine blessings). Just because a few select athletes, actors, podcasters, and musicians continue to succeed in their careers while under the influence of *chronic* concentrations of THC does not mean you will too, for they are carried in their careers by caregivers; their coaches, producers, booking agents, cohosts, & wealth (Environmental Enrichment), whereas you, you my friend will likely only have your spouse and children to rely on when you become too old to think clearly, to think creatively, and to work efficiently, and if they abandon you, all that you will have left is your intelligence, that of which is a power that if dampened through excessive drug use will destroy your survivalism potential.

As a preemptive response to those who suggest that the errored thinking THC causes is a form of creativity that is capable of stimulating profound and intelligent lifestyle changes, this is only a partial truth, as creativity formed in the presence of neurotoxicity *and* errored memory formation (memory acquisition dysfunction) will only result in destructive and illogical thought formation and continuation. Most creative ideas form in the mind after sleep, or after waking and willing deep thought (as Poker players say; Tanking), the inability to comprehend what is error, and what is possibility will only lead to purely delusional thinking. If short or long term memory is impeded, even if one or more novel creative thoughts (uncathected neurons: unconscious neuronal activation) are generated and actively being facilitated, the possibility of success will diminish substantially due to inherent cognitive weaknesses. The 21st Century teenager who abuses THC, Nicotine, Caffeine, and Alcohol, may very well possess a high level of creativity, but it is incomprehensible and useless, as evidenced by their regressive humor and any art that they generate being too strange, perverse, or abstract to be understood, this is what is referred to as “Brainrot”, an apropos term to described pathologically regressive thinking. Brainrot is not only a side effect of recreational drug use during neurodevelopment, but the result of a cultural nihilism. If a child is not allowed to embrace a scientific study due in part to being *graded* in school as intellectually inferior, they will find freedom in escaping to fictional worlds, those of which lead to a disconnection with reality, and the tendency to embrace chaos and regression.

Recreational drugs are in my opinion useless if not utilized for analytical or physical performance enhancement, and it is unfortunate that first world nations allow their children to become addicted to altered states of mind without intellectual creation, and this issue may be arising from our societal addiction to fictional hyperemotional works of art, unfettered consumerism, coupled with ever decaying and deranging morality. We must ask ourselves even when we consume something as seemingly innocuous as a cup of coffee why we are about to use this exact drug, what will it help us accomplish, how

will it help us become healthier, stronger, faster, more enduring, wealthier, or smarter? If it's simply a habit devoid of application towards intellectual or physical ventures, its clearly wasted potential, a wasteful loss of neurons, or neurites.

Exercise Equipment High Technology, Free Weights, & Concentricity

High Technology in my mind means technology that is not necessary, a luxury sold to those who dream, rather than live through action. An example of this is the newest Variable Resistance technology and exercise equipment, where a novel small and portable device is capable of changing the loads intra-repetition such as during eccentric overload, or partial-ROM overload (chains, bands). Though this technology is exhilarating in thought, it is meant for the least informed fitness enthusiasts, as no singular device will be able to accurately mimic the motor patterns, and train or facilitate the motor memory intelligence necessary to engage in the variegated tempo, ROM, or resistance changes that free weight use results in.

Even with the most advanced and futuristic training equipment—the high technology of our century—a person will not be able to surpass their more archaic contemporaries, those who use bodyweight exercises, and free weight exercises. The introduction of novel training methods that change the aforementioned variables to those who have not mastered compound lift exercise form, or have come to understand the necessities of deloading, detraining, and stem cell limits (the natural limits of myogenic recovery based on the use or absence of use of steroids, myogenic modalities, and myogenic supplements) will do no good for a person, and only give them the illusion of physical progress. Now if these individuals strength train for fun rather than for performance or size gains, this new form of exercise technology will give them a large amount of pleasure, but for those who chase after absolute power, strength, or hypertrophy, they will only end up overtraining through the addictive nature of high load lifting combined with motor pattern experimentation.

It does not make sense to give a man or woman access to a device that allows them so much exercise variation, and tension variability, when they are unprepared, and ignorant of the function and purpose of each variable, and considering the steady rise of tempo training popularity, as more tendons rupture, and severe muscle tears occur, due to foolish social media coaching and personal training, the existence of *too much freedom*, of *too much exercise type / technique variability*, will harm those who with undeveloped bodies and minds. We all start our motor-myogenic journeys by crawling, then walking, then running, and finally squatting, and in the simplicity and safety of high volume concentric contractions comes the refinement of the mind and body, and the necessary preparation for far less common, and unnatural forms of training.

This criticism of Exercise Equipment High Technology is not solely aimed at Variable Resistance Training devices, but also all of the premium, multi-use, hypercomplex

exercise apparatuses that companies sell predominately to customers who use them for purposes unrelated to gaining a competitive advantage in physical sports, and instead treat them as toys, which is not inherently wrong in my opinion, but regardless it results in confusing new lifters into believing that dumbbell lifts, plate loaded barbell lifts, and bodyweight resistance training exercises are insufficient for the maximal promotion of muscle growth or performance.

As the evolution of fitness equipment continues, new training apparatuses will continually emerge and cost an increasingly greater price. If you are like me and prefer to train at home, due to the lessened sensory stimuli, and the total freedom of exercise form, dress, and timing (many gyms close too early for my liking), you may think that if you could just purchase a certain piece of impressive and complex exercise equipment, your dreams will come true, but this a delusion, as until you master through massive amounts of concentric volume the four compound lifts, exercise warmups, bodyweight exercises, and LAT with free weights, you will be undeveloped physically and mentally, and should therefore save experimentation with novel pieces of exercise equipment, high load extreme tempo training, or any Exercise Type beyond static contractions, for the point in time in which you have overcome life's boring but essential concentricities.

On Willpower

When I was younger, due to a combination of three factors, my total testosterone was at one point around 50, which is the equivalent of a very sickly elderly man, or even a woman, and this was due to two primary contributing factors. Firstly, I was addicted to carbohydrates, and various junk foods, I used sugars and fats as drugs to cope with the second factor—chronic unpredictable stress, that of which I experienced unrelentingly in school as a child, and in another form during my formative teenage years for a wholly different reason. I did not have the motivation, the hormonal energy, or the confidence to work out during my earliest life, although I dreamt of being as large and intimidating as all the bodybuilders I worshiped growing up, those being Arnold Schwarzenegger, Sergio Oliva, and Dorian Yates. I dreamt also of being strong and powerful too, like Zydrunas Savickas, and Bill Kazmaier. Although I did not workout often, I did develop an interest very early on in researching simplistic training methodologies, and basic exercise sciences, as intermittently studying how to exercise was far easier for me than going out into the real world, and building my body and mind through actual exercise, which I was fooled into believing required a gym membership, and some form of sociality.

Because I became at some point in my teenage years, obsessed with the World's Strongest Man competitions, as I realized unconsciously that there is no better defense against bullying than physical strength and power, it was during this period of time that I began to exercise more frequently, but still very rarely, maybe three or four days a month. I would go into a gym and train like my idols, and lift the heaviest weights I could

manage, and although these workouts improved my confidence, they were insufficient for promoting the quality of life improvements I needed. It was only into my late twenties, after having sustained numerous small and large musculoskeletal injuries from overtraining, attempting to mirror the training loads, intensity, frequency, and volume of the bodybuilding, strongman, and powerlifting men I looked up to, that I came to the conclusion that all of these heavy weights I was lifting was illogical, and so I began to train with 2LB dumbbells, first out of necessity (injury), which after performing countless repetitions lead to the formation of a strong whole body mind-muscle connection, wherein I stopped Unconsciously Lifting, which ultimately lead me to the clarity of thought—the understanding—that you don't need a high testosterone, or steroids to build muscle, or to train hard, you just need willpower and a little bit of intelligence, coupled with some form of Ego Death (not caring anymore if people think, or see that you are physically weak). I began to perform three or four hour whole body workouts in my local gym with light weights, of which to you the reader would be considered extended IMC exercise warmups. These workouts were composed of dozens of exercises, compound and isolation, and due to the low loads lifted, the high volume entailed in each exercises set, and the supreme focus I exerted to use controlled form each repetition, this became my low-moderate intensity interval training, my cardiovascular training, my Lactic Acid Training, and this began to improve not only my confidence, but my mood and my memory. Yet had I instead embraced a cardiovascular exercise specialization, I would possess a far higher intelligence quotient at this point in time, and I would be far more successful career-wise, but my high volume thorough warmup workouts introduced me to the power and sustainability of light weight training and low intensity cardiovascular exercise, as many exercises that I performed with my light weight dumbbell's resulted in an intermittently elevated heart rate, and the generation of large amounts of lactic acid of which I could feel saturating my damaged neurons.

Even as an older man, with a proper diet, and a normal testosterone, I still know my bodies limits—I know my stem cell limits, and there is something special about finding that limit, and working within it, although it may seem constraining, and at times unfair to train within your physiological limits, to lift lighter weights at a very high frequency, to take more time off between hard workouts, to put your obsessive and carefully planned workout protocols on hiatus, or scale back your training frequency – volume – or intensity, these are all essential components of maintaining healthy skeletal muscle, tendons, and joints into old age.

The muscle mass I have built thus far in my life has not been from my choice of exercise load, volume, or even supplementation, it has been through sheer willpower, the willpower to resist the cellular decay caused by psychological stress and hormonal deficiency. I understand how it feels to be tired, to be weak, and to be brittle, which is why I have been so adamant, and *repetitive* about my strong suggestion that training with lower loads, and engaging in more cardiovascular exercise, is so very important. The

more you train, the better you feel, the better you feel, the more you train, this is the cyclical nature of health and fitness, and this is why you should, and you must train with lower loads more often than not, for nothing is more sustainable and more beneficial than this. Although many bodybuilders and intelligent fitness thinkers such as Charles Poliquin, the man who created the term “Time-under-tension”, have discussed the benefits of high volume resistance training for years, their form of “high volume” resistance training involved higher loads, and an insufficient number of repetitions. Training with light weight in my opinion does not mean going into the gym and bench pressing 50LB’s for thirty reps to failure, it means bench pressing 5LB’s for one hundred repetitions to failure.

Because when I was younger, having trained and existed within a physiological system of stem cell impoverishment, I have developed a significant empathy for the elderly, and older women in specific, many of whom must exercise at a significant cellular disadvantage, and are fooled by enhanced fitness influencers into believing that they don’t train “hard enough” or “heavy enough” to grow muscle, or burn fat which is why I no longer trust nor respect powerful fitness personalities, the men and women who train others in and from a place of myogenic ignorance. Those with hormonal deficiencies, or those with *anabolic hormonal discrepancies*, such as females, must be taught that they too can become healthy, strong, and fit if only they learn the power of high volume light weight training, dietary manipulation, and over-the-counter chemical / prescription drug abstention.

Music is Language *x* Sensation

"When modes of music change, the fundamental laws of the state always change with them".
The Republic: Book 4: 424 c.: Plato

We all understand music to be a form of communication, as lyrics are poetic expressions of repressed thoughts, or feelings, but beyond lyrics there are notes, rhythm, cadence, and tempo, and these variables of music rendition, although being understood as more abstract expressions of emotion, or feelings, are not often understood consciously as also carrying tangible and decipherable diction of meaning and intent, of words that resonate within the artists heart. At some point in time through sophisticated artificial intelligence analysis instrumental musical pieces will be able to be deciphered into visual images, and then words, and this is because just as spoken words associate with images, of symbols, so too can these musical components be understood as symbols.

The instrumental music with the greatest complexity, and depth of meaning, of decipherable language, is sure to be Electronic music, and by proxy Classical music, and all of their derivatives, for these artists communicate through their fingertips in a far more

complex degree than the alternatives, such as rock music, metal, or rap. It is for this reason that many people hold great disdain for Classical Music, and strange and complex Electronic music pieces, for their messaging although not being understood consciously, is unconsciously understood, causing anxiety due to the sheer complexity and density of thoughts transmitted. In terms of Classical music, which is the least popular music of this generation, it is no coincidence that as our society regresses in instinctual life towards hypersexuality and hyperemotionalism that certain styles of music, certain messaging contained within the flow and composition of instrumental music causes them to feel anxiety, as this messaging does not align with their social programming. You cannot logically argue that Beethoven's Moonlight Sonata does not perfectly align with the perceived psychosocial stress he experienced growing up due to abuse by his father, and this tremendous piece of expression does not only carry with it an abstract emotion or feeling, as these phenomenon's are after all only derivatives of thoughts, of visual and audio memories colored by stress hormones, connected together to form symbols.

The increasing vapidity of music is a sign of the loss of intellectuality among young people, where extremely simplistic and repetitive meter and flow is used in so many different songs. We see today the overreliance on lyrical-based composition, which although to some would be appear to be an evolution in music towards greater comprehensibility and transfer of messaging, is in fact a regression to childish forms of musical rendition. This is because a child master's his or her verbal faculties long before his motor faculties, making instrumental music, especially with hypercomplex instrumentation, flow, and meter, the more evolved form of musical creation.

The sexual revolution was not paralleled by hypersexual rock music, it was facilitated by it, because music is, as Plato suggested, capable of changing the (moral) laws of a state (country). The rhythm and beats of rock music, even those without sexual lyrics, paints a picture of the rhythm inherent in sexual acts, and if you think this insane, consider how many rock musicians will admit that they entered into their profession at young age to "get girls" , thus lending credence to my idea of instrumental music being decipherable by far more than abstract phenomenon, but instead words, and images, mirrored and translated into signals and vibrations that stimulate and remind us of certain physical sensations.

Metal music, associated with the expression of violent anger, and violent despair, is clearly the *Freudian Musical Death Drive* in full force, where the sexual frustrations and antisocial tendencies of metal fans drive them to experience hysteria, that of which is molded into a comprehensible but sublimated psychological vibrational message of abstractly projected anger, despair, or fear. The tones and rhythm of Metal music illustrate a story of suffering and unhappiness, and the motor release of sexual frustrations, because it is quite clear to me that metal heads are in fact merely the nerds and geeks who were not given proper education, who did not find their hard science to

embrace when growing up, and instead happened down the path of motor expression, its cathartic release being too alluring to avoid.

This generation of Rap music is in my view the most regressive form of music, considering as aforementioned its simplistic compositional elements, and repetitive beats, where the overuse of sub-bass (20-60Hz) is a regression to the earliest audio and vibrational sensation memories of their life in their mother's womb, her heartbeat, as a babies ability to hear their mothers heartbeat can occur as early as eighteen weeks into gestation, and they experience the vibration of their mothers heartbeat at an even earlier period of gestation due to the facilitation of sound waves by way of amniotic fluid. This regression may seem a severe and extremely large psychoanalytical logical leap on my part, but it is explainable precisely because their choice of and dosage of drugs, chronic THC to be exact, as this causes far more synaptic chaos and unconventional thinking than the alternatives, where the most ancient memories are unlocked to the consciousness, thus resulting in the incorporation and the predilection for repetitive and obnoxiously noisome sub-bass inherent in modern rap and its fans, especially the sort with vapid-nonsensical lyrics.

I believe it is necessary for those who desire to become both mentally stable and intelligent, who have become addicted to simplistic and hyperemotional forms of music, to force themselves to attune their brain waves to higher forms of musical rendition, such as through listening to Classical, Piano, or Ambient Music, especially during periods of intellectual pursuit. Regardless, there is not error in listening to simplistic hyperemotional music of any genre if it helps you maintain a BPM range during cardio, or if it helps you to maintain time-under-tension during resistance training and overcome the pain of lactic acid generation, while it becomes a danger to play music that stimulates certain negative, libidinal thought patterns during high load training, as you may end up training beyond your bodies abilities and become injured.

The Aged Microbiome

We understand that the human body ages through senescence, but what of the gut microbiome? Is it possible that our cellular decay mirrors our microbiome decay, in that as we age, our beneficial bacteria die off? Beyond extracellular vesicles, and beyond dietary changes, it must be true that due to natural changes to intestinal tissue, its functions, that during aging the good bacteria that line our gastrointestinal tract begin to find greater difficulty towards surviving, towards proliferating. Is it not possible that this *microbiota-based failure to thrive* leads to the expedited death of their hosts, their human conduits, through accelerated senescence, specifically immunosenescence, and the inevitability of cancer metastasis? We know that when Bacteroidetes begin to dominate the microbiome, sickness is never far off, and this is due not only to our addiction to simple grains, sugars, and processed foods, but also the natural trend of gastrointestinal aging. The cultures with the most centenarians often consume the greatest amounts of

fermented foods, and this is not a coincidence, nor is it explainable by *only* the increased consumption of vegetables, and soluble prebiotic fibers, it is directly related to the replenishment, or dietary probiotic-induced alteration of their microbiome—the mutual facilitation of beneficial microorganisms, as many fermented foods contain organisms that are often unrelated to Lactobacilli or Bifidobacterium strains, but nonetheless promote their growth indirectly through reducing the growth of pathological microorganisms. Life extension therefore may be as simple as this heuristic algorithm:

$$LE \propto \frac{\text{(Essential Nutrient consumption } x \text{ Probiotic use } x \text{ Fermented food consumption)}}{\text{(Simple grains, and Microbiome Toxins such as Processed Foods, certain pharmaceutical drugs, OTC drugs, or even quite possibly recreational drugs)}}$$

We know that when beneficial bacteria die, systemic inflammation increases, which if combined with exercise may be partially utilized to grow muscle mass, or accelerate early wound healing, but during aging this inflammation becomes pathological, and even though I believe that chronic exercise may partially counteract this, especially low intensity Endurance Training (60-65% Max HR), that of which is immunostimulatory, only time and more research will be able to elucidate on this. For many, a good diet is enough to extend lifespan, and maintain strength into old age, but for others a good diet is too inconvenient, or too tasteless to maintain.

I'm certain that with the increased consumption of fermented foods, and the increased use of probiotic supplements, a human body can become far more resilient towards macronutrient excess than their counterparts, but what is the point in attempting to restore or protect the "Second Brain" while sabotaging it to such a great degree with a bad diet? Selfsame to vegetable juicing, where you will attain rapid benefits from it, you will also lose out on the long lasting benefits of vegetable consumption by not eating more raw colorful vegetables each day, by making it a habit to eat good each meal, rather than periodically. Many people assume that they can counteract or delay their cellular aging by taking expensive supplements, but even in the case of premium organic and fermented grocery foods, we must begin our journey towards optimal health by abstention of the worst foods, long before the adherence to a diet of the very best foods.

The World (of Detraining) is Not Enough

I have heard Dorian Yates discuss the necessity of Detraining for anabolic growth, and although I respect him more than most bodybuilders, for he was one of the first to popularize "negatives", that being a focus on the eccentric aspect of weightlifting. He, and many others, unfortunately do not understand that a heavy reliance on Detraining is not suitable for a natural lifter, not for long periods of time, and this is because firstly, the stem cells an enhanced bodybuilder produces after an intense high load workout will be much more numerous as compared to their natural opposites, meaning the longer they

rest after a workout, the greater myogenic potential there exists for the maximization of hypertrophy. This does not mean a natural lifter should not detrain, it means that the benefits they will attain from detraining will be much less noticeable regarding myogenesis. Furthermore, considering the commonality of overtraining, where people who are not athletes spend hours in the gym lifting heavy weights, assuming that more muscle damage equates to more net muscle gain, detraining for an extended period of time may reduce the risk of injury by a small amount, but it will never overcome the anabolic benefits of training with optimal volume—of training by and for individualized human stem cell magnitudes. Separating high load workouts by specified periods of recovery days is essential for a powerlifter to continue to gain absolute strength in the gym, or a ET:SS trainer to recover their tendons and soft tissue between workouts, but it is not as anabolic as we would hope, and in scenarios wherein a person lifts too heavy, too often, and detrains excessively, muscles will surely age far faster, due to accelerated senescence, or capillary regression, thus making low load training essential for those who choose to lift the heaviest weights, and the inclusion of ARCS a necessity to delay whole body aging. The less you train a muscle, the greater it may grow, if training volume and tempo are controlled, but this does not make high load training combined with scientifically programmed extended detraining *healthy* options, especially not for a natural lifter who will grow such little muscle from strenuous training. As I have said before, and will say forever, low loads should be lifted more often than high loads, especially if your life does not revolve around absolute strength, nor the highest levels of competitive muscular output.

One must understand that detraining will not substantially reduce the chances of injury occurrence when the loads lifted during reloading are too heavy, and the volume is too high, as the primary purpose of detraining is merely to facilitate the growth of muscle tissue, not to treat or prevent injuries, leaving aside ET:SS for the purposes of tendon strengthening, there is of course carryover here, but my argument remains valid. If a workout damages a muscle beyond the body's ability to hypertrophy said muscle, only the longest periods of detraining will be able to compensate for the lost tissue through myogenic differentiation, which is an extremely time consuming, sensitive, and often inefficient process.

If you constantly detrain a muscle to the maximal extent, without unintentionally utilizing them at work through hours of aerobics, or at the gym through antagonist muscle stabilization activation, or highly technical low load resistance training exercise, or cardiovascular exercise, you will shorten both your lifespan and your musclespan (a term I coin to mean muscle tissue senescence and health), and this is why I suggest you reserve high load resistance training for periods in your life wherein you have the greatest *anabolic opportunity* to grow, when you're consuming the most protein, carbohydrates, and fatty acids, when you're using the most anabolic supplements, and engaging in the greatest amount of myogenic modality therapy, whereas it is essential that during the majority of your life, most especially if you are unenhanced, that you ensure you are consistently aerobically training your muscles, to counteract muscle atrophy, capillary regression, and senescence, and to temper your mind through endless repetition.

Errored Divergence

If dreams are simply a way for the brain to process interpersonal and intrapersonal emotional, sexual, & analytical errors encountered in waking life, and many people are stimulated by their dreams to pursue drastic changes to their lives, we can consider dreams essential components of consciousness, and free will. Through our nighttime error processing, storylines are formed that have never existed before, and the majority will never exist again, and although the profound storylines, the censored messaging, or wishes of these dreams break down during complex examination of their meaning, or meanings, the early and most simplistic analyses of our dreams can hold such power over our lives, and this is not always towards the facilitation of delusional ends, for even the most intelligent thinkers on the planet, those who have built companies from the ground up to reach billion dollar worth, or have invented novel technologies have dreamt, and have remembered their dreams, meaning that dreams are a prerequisite for a certain form of creative thought divergence, and I understand that the sicker a person is—the more ongoing neurotoxicity and synaptic chaos present—the more censored, disfigured, and incomprehensible their dreams will be, meaning that some dream storylines are applicable to real life, while others are too strange to result in intelligent inspiration.

It is not always necessary to analyze a dream in depth, as they often will lose their luster—their inspirational or profound message. Censorship is a necessary component of a healthy and happy society, just as it is for a healthy and happy mind. If we were to dream only of our desires coming to completion, without synaptic filtering and disfigurement, and a melding of numerous thoughts, feelings, and memories both new and old, we may very well lose our humanity, and our morality, for to error is to live. But it is also true that too much censorship is deleterious for the intelligence and wisdom of a collective society, and an individual mind, as no truth will be found when delusional thinking supersedes logic. Therefore, we must allow the bulk of our dreams to exist as a way for us to escape the often brutal and cold logical confines of our realities.

Dehydration Confusion

I have always found it strange how many Endurance Athletes, such as Cyclists and Runners, consume such little water during training, and I began to think of the effects of dehydration on cardiovascular exercise muscle adaptation and responses. In terms of Endurance Training specifically, if an athlete is to engage in an hours long workout in a dehydrated physiological state, would this not result in enhanced catabolism? Considering H2O molecules are required for lipolysis to function within the mitochondrial machinery, it can be logically deduced that in the absence of sufficient H2O molecules, lipolysis will be blunted, leading to enhance catabolism in energy deprivation scenarios (fasted exercise), but what if a sufficient amount of fast digesting carbohydrates are consumed pre, or intra-workout, will this not blunt the catabolic response of dehydrated cardiovascular exercise?

There is no doubt that the majority of Endurance Athletes function well enough in a dehydrated state, but what would happen if they substantially increased their intake of water intra-workout? Firstly, with sufficient hydration comes frequent evacuation, and this is clearly not ideal for an athlete who competes in timed competitions, but regarding the muscle tissue, if an athlete is extremely lean and trains in a dehydrated state and lipolysis is blunted, what happens if he or she consumes a sufficient or excess amount of H2O intra-workout, what exactly happens within the mitochondria? I believe that in scenarios where adipose tissue is not an available resource, or plentiful enough for the body to sequester energy from, that the process of lipolysis is still perturbed, meaning that from a purely energetic standpoint proper hydration may due an Endurance Athlete who is extremely lean little good, but what if they consume a surplus of fatty acids pre-workout, and post-workout, then it becomes interesting. The surplus of circulating fatty acids in the blood of Endurance Athletes would surely be utilized in lipolysis, and proper hydration would only further enhance the metabolism of these fatty acids, therefore we can say that if someone is focused purely on Endurance, that consuming pre / intra-workout fatty acids (MCT oil, & Coconut oil especially), if paired with large amounts of water, that they may outperform their contemporaries, that is if their muscles have been conditioned and transformed into a predominately slow twitch phenotype. Conversely, if an athlete is to consume large amounts of fatty acids, and remain in a dehydrated state (as many Endurance Athletes are prone to doing), they will attain little to no benefit to performance, as lipolysis will be blunted due to the lack of the resource H2O, and performance may even be harmed.

Leucine Cycling, Fast / Slow Specializations, & The Protein Myth

If you have read my section on Unmentioned Amino acids, you know that excess Leucine intake does not stimulate myogenesis as much as an adequately high intake of Essential Amino acids, as it will compete with entry into cells with adjacent amino acids during the process of Protein Synthesis, and that it may be a better idea to reserve supplemented and purified Leucine for periods in your training where you are focused on slow twitch fiber growth, as Leucine appears to not only stimulate mTOR, but predominately promote slow twitch muscle fiber growth. Continuing in line of this logic, we could say that during periods of Endurance Training, Aerobic Training, Endurance (Yielding) Isometrics, it may be intelligent to restrict protein intake in favor of copious amounts of supplemented Leucine consumed pre / post-workout to further magnify slow twitch fiber growth. Conversely, during periods of fast twitch training (Regular-speed Strength Training, Powertraining, HIIT (Cardio), Superslow Eccentricity Training, or banded Speedwork), every essential and *non-essential amino acid* (except for Glutamine), would be consumed in chronic amounts, to promote both slow and fast twitch fiber growth.

Because Leucine stimulates Sirtuin-1 expression in skeletal muscle cells, and is a slow twitch fiber anabolic amino acids, it is possible that the temporary restriction of other amino acids during the day while singularly supplemented Leucine may promote longevity in our muscle tissue. This *Leucine Cycling* idea, attributable to Robert R. Wolf:

Reference: [479], could be easily actuated through consuming a Leucine (+HMB) shake every three or four hours, and especially pre / post-workout, while consuming adequate or lower amounts of slow digesting food protein each meal, ensuring that you avoid using any and all protein powders.

It is intelligent in my view to experiment with both *Fast* and *Slow* muscle phenotype cycles of training, diet, & supplementation into your life which will result in noticeable changes to muscle growth and muscle fiber typology. As previously mentioned, if you are on a Slow Phenotype Specialization you focus on Aerobics, Endurance Resistance Training, Endurance Isometrics, and Light-Moderate Load Concentric-only Superslow Training, while consuming large amounts of MCT oil, restricting your carbohydrate intake to facilitate a long lasting glycogen depleted physiological state, and using ergogenics that promote PGC1a expression or promote Fast-Slow conversion such as L-Theanine, BHB, Agmatine, Citrulline, Nicotine, and Melatonin to name a few compounds. And if you are on a Fast Specialization you will focus on Light-High Load Eccentric-only Superslow Training, Regular-speed Resistance Training, Resistance Band Explosive Training, consuming large amounts of Lauric Acid & Nattō (Toll-like 4 Receptor activators) and Carbohydrates all day (especially an intra-workout liquid sugar drink), and supplementing EGCg or low dose THC as CB1r agonists.

Although cycling between Fast and Slow Phenotype Specializations will in all likelihood eventually result in a far greater, and far stronger density of slow twitch fibers due to muscle fiber transformation, this will be a good end result, as slow twitch fibers are far more resilient to apoptosis and damage than their ephemeral but large brethren.

The Protein Myth is often spread by fitness influencers who suggest that without a high protein diet, a person will not grow any muscle tissue, as protein is necessary for muscle growth, but this is actually untrue. If you go to an African nation, and find an impoverished mine worker, one who engages in physically demanding labor nearly every day, and you shake their hand, you will be surprised by how strong their grip is—how strong their forearms are. Do you think that they drink whey protein isolate, and BCAA's during their daily work? Do you think they go home and eat a large chicken breast with a heaping portion of white rice? Clearly, not. These men who exert themselves relentlessly to feed their families engage in strenuous exercise on an empty stomach most often—in a hypoproteinemic state—and yet they still accrue impressive physical strength, and this aligns with the research mentioned before that shows amino acids are in general, leaving aside a select few like Leucine, predominately anabolic towards fast twitch fibers. Although one could argue that fasted exercise, or protein-deprived exercise, only promotes strength gains because of neuromuscular junction improvements, this is only part of the equation, as the strength that these extremely hard working men possess is *enduring*, it is slow twitch, therefore whether they have accrued a large amount of blood vessels in their upper body muscles, or whether they have simply overtrained their muscles to the point of slow twitch compensation and slow twitch phenotypic domination, they have still grown their slow twitch fibers. Does this mean we should restrict amino acids on Slow Specializations? No, but it does mean that muscle growth

and diet are nuanced sciences, and one cannot simply suggest that “protein is required for muscle growth”, instead it is “protein is required for fast twitch muscle growth, *and* protein synthesis (muscle maintenance: maintained hypertrophy / reduced all-fiber-type muscle tissue degradation)”.

Time Sensitive Caffeine Dosing

Caffeine has a very long half-life, as you should understand by now, and considering that it is neurotoxic, even if subtly, the very most intelligent way to use it is relatively acutely, within the first hour or two after waking up, alongside programmed morning cardio, or warmups. Even if the dosage of caffeine is relatively high, such as 300mg, or 400mg’s of caffeine coming from Green Tea, Coffee, or Caffeine pills, as long as sufficiently intense morning exercise is performed, and a high protein breakfast is consumed, contrary to expectation, you will feel far better and sleep much more soundly in the night, as this this morning Time-Sensitive One-Two Hour Caffeine dosing schedule will ensure that your blood levels of caffeine will drop off steadily throughout the day, to protect sleep hygiene, and prevent unnecessary neurotoxicity.

One may argue against this morning-only dosing schedule that they will experience a psychological “crash” in the afternoon, and require another dose of caffeine, but this is nonsense as the return of adenosine receptor activity will only occur in the evening hours if the dose of caffeine administered in the morning was sufficient (250mg +), and this is good, because if you aren’t exhausted and tired by the evening, you’re clearly doing something wrong. If you do experience a loss in energy in the afternoon, and your morning acute caffeine dosing, this is more likely to be a sign of hypoglycemia, or psychological stress. The act of sipping multiple coffee’s each day does not promote wakefulness more than consuming one shot of espresso, it is merely an addiction to sensory flavors; sweetness, creaminess, a dopaminergic rush.

Even with Time-Sensitive Caffeine Dosing, it is still essential to take two days off per week where you give your body a full termination period for any remaining caffeine in the blood, which is around 72-Hours. Doing so will allow you to experience the greatest eugeroic and lipolytic effects of caffeine, while avoiding excessive neurotoxicity, and sleep cycle perturbation.

As an example of this in action, I sip Green Tea (10-12 Bags: 300-500mg Caffeine) on Mondays, Tuesdays, Thursdays, and Fridays immediately upon waking while performing my morning low intensity cardio. After my morning LIT is finished, I ensure my Green Tea is finished (this is my one hour caffeine period). After this hour or so of Tea + Exercise if completed, I deprive myself of any caffeine for the rest of the day, and I do not crave it, as my blood levels are sufficiently high.

Ephedrine Chagrin

Ephedrine became a popular fat burner in the 90s, until an FDA crackdown occurred,

where it no longer became legal to sell it in supplement formulations, although strangely, Ephedrine is currently still available to purchase at pharmacies, without a prescription, but it is sold behind the pharmacy counter, and requires an ID to acquire, such as the popular bronchodilator brand Bronkaid, which contains tablets made of Ephedrine Sulfate.

The crackdown on Ephedrine-based dietary supplements is in my opinion based on a logical premise, that being that Ephedrine can raise blood pressure, and increase the risk of heart attack or stroke through its beta-adrenergic receptor agonism, but this cardiovascular danger is overblown, considering even caffeine can increase the risk for heart attacks due to vasoconstriction, and yet we do not control a person's intake or possession of it, and with the rise in THC legalization, cardiovascular fibrosis and heart attack incidence will only increase. If someone in the late 1990's, who was using Ephedrine, experienced a heart attack, I am willing to bet in the majority of scenarios, that this person was using the "ECA stack" Ephedrine-Caffeine-Aspirin, which owing to the caffeine content, and the inclusion of the COX2 inhibitor, is liable to significantly increase the risk of cardiovascular events, and post-event cardiovascular damage (remember some level of COX2 is necessary for cardiovascular health). I do not believe that Ephedrine alone is as dangerous as the Government and media purported it to be, especially if it used during periods of frequent moderate intensity cardiovascular exercise, and its use is cycled intelligently, but if one is to use it during periods of high load resistance training, minus the cardio, while already suffering from high blood pressure, this is obviously dangerous.

It appears that the true danger of Ephedrine is the unnoticed neurotoxicity is associated with its use, leading to progressive brain damage, but this effect appears to be related to hyperthermia[1], which is potentiated by Aspirin[2], thereby exacerbating the risk for neurological complications. This information leads me to think that if Ephedrine were to be used for lipolytic purposes, it would be best treated as a Caffeine-substitute, never used in the presence of NSAIDs, never used alongside Hyperthermia Therapy, and only taken, similarly to CLA, for very short periods of time to reduce the risk of brain damage.

"<>Multiple doses of the dietary supplement L-ephedrine can cause severe hyperthermia and modest dopamine depletions in the rat brain. Since D-amphetamine treatment can result in neurodegeneration, the potential of L-ephedrine to produce similar types of degeneration was investigated.
<>Adult male rats, some implanted in the caudate/putamen (CPu) for microdialysis, were given four doses of 25 mg/kg L-ephedrine or 5 mg/kg D-amphetamine (2 h between doses) at an ambient temperature of 23 degrees C. L-ephedrine-induced degeneration in the forebrain was dependent on the degree of hyperthermia. Layer IV of the parietal cortex was the most sensitive to L-ephedrine treatment with peak body temperatures of at most 40.0 degrees C necessary to produce degeneration. Extensive neurodegeneration in the parietal cortex after L-ephedrine treatment was as pronounced as that previously described for D-amphetamine treatment and also occurred in the intralaminar,

ventromedial and ventrolateral thalamic nuclei in rats with severe hyperthermia (peak body temperatures>41.0 degrees C).
<>The neurodegeneration induced by L-ephedrine may have resulted in part from excitotoxic mechanisms involving the indirect pathways of the basal ganglia and related areas. No differences were observed between microdialysis and non-implanted rats with respect to degree of tyrosine hydroxylase (TH) loss in the CPu after either D-amphetamine or L-ephedrine treatment. However, neurodegeneration resulting from D-amphetamine and L-ephedrine was reduced in the microdialysis animals in the hemisphere ipsilateral to the probe, which raises concerns when using the technique of in vivo microdialysis to evaluate neurodegeneration.
<>The results of this study, in conjunction with human clinical evaluation of ephedrine neurotoxicity, indicate that regionally specific damage may occur in the cortex of some humans exposed to ephedrine in the absence of stroke or hemorrhage."[539.6B]

"<>Chronic administration of aspirin to obese mice had no effect on energy balance and body composition. In contrast, ephedrine increased energy expenditure by 9% and reduced body weight and body fat by 18% and 50%, respectively: obesity, however, was reduced but not reversed. In the presence of both ephedrine and aspirin, increase in energy expenditure found during treatment with ephedrine alone was doubled, and the obese group lost greater than 75% of body fat: obesity was reversed. These studies indicate that although aspirin administered alone has no influence on energy balance it can markedly potentiate thermogenic properties of ephedrine, effects which led to a normalization of body composition of the obese to that of the lean. Such ephedrine-aspirin mixtures, often found in over-the-counter preparations for asthma and bronchial disorders, could be put to new use as aids for treatment of human obesity."[539.6C]

Mathematical Disbelief, Materialism, & Zero-point Thinking

As I was working on formulating a workout protocol that begins at Week-1 and ends at Week-4, followed by an immediate switch to a similar but different four week protocol being pursued, I came to the realization that counting from Week-1 to Week-4 is unbalanced, as if you count properly, Week-1 to Week-4 is actually three weeks, not four, yet counting from Week-4 to Week-8 is clearly a balanced four weeks, so what is wrong with starting the protocol at Week-1? Well, it's actually because the protocol starts at Week-0, the zero-point, the beginning, and only when we start at this zero-point do we find balance, 4-Days (0-4) and 4-Days (4-8). This is a simplistic but profound error in cognitive indexing that goes unnoticed by the majority of the world, except by high ranking computer scientists.

We are taught in school to begin counting at one because a young child is not able to grasp the idea of absence, of nothingness, of the incomprehensible, but one is not the beginning, and in this error comes the enhanced risk of psychological attachment in adulthood to materialism, and the inhibited ability to engage in creative (abstract) and

philosophical thought, including forethought, because we either forget, or never learned that the starting point of all numbers, of all life, of all reason, is zero. If we consider the number one as the starting point of all numbers then we are falsely assigning a timeless and immortal value to *somethingness* , rather than *nothingness*, and this tricks us into believing that the universe was always in existence, that matter has always existed in some form, that life is an endless and futile basic helix-loop-helix. Whether this zero-point is metaphysical nothingness, or the memory trace of an omnipresent God, is irrelevant, the point is that the development of intelligent abstract thinking, of advanced forethought, what I believe is true intelligence, is impeded in children who are not taught the importance, the power, and the natural origin point of the number zero.

Children who are innumerate are often blessed with enhanced creatine thinking, but not necessarily effective forethought, and this is not due to being innumerate, but instead related to suffering from synaptic dysfunction, or other brain connectivity issues. As I have alluded to before, and will do so again, a brain (system) that does not operate perfectly is more liable to overcome the confines of purely analytical thinking, but this is only useful if the abstract thinking is paired with an analytical subject, for there are many who daydream of impossibilities (emotional works of fiction), but the daydreamer who grasps the boundaries and complexities of a particular science has the potential to accomplish amazing works.

For those who would argue I am incorrect, and suggest that any workout protocol that has a beginning should and must "begin" at "Week-1", are in fact confused, as any workout protocol that has a beginning, must start at the zero-point, and not be collated from zero-to-one. Furthermore, through discussing my idea of Zero-point thinking with ChatGPT, I have been told that it is made far more plausible by the existence of Construal-Level Theory, created by Yaacov Trope and Nira Liberman, which describes and separates the abstract - absence thinking: the "why" of thinking, versus the "how" of thinking, for example it would be a high-level construal to think of *why* exactly you chose your current workout protocol, versus a low-level construal to think of *how* to follow your current workout protocol. In this hypothetical view, a child raised through Zero-point thinking would be more liable to engage in high-level construal, leading to a far greater ability to engage in creative forethought, as the first concept that should be understood by a child, in my humble opinion, is the first psychological lesson, the comprehension of the abstract world.

Although One-point thinking may seem like active forethought, since we are overestimating the future by adding one unit of measurement, it is unfortunately illogically applied forethought that only results in the development of psychological impatience, and a distorted sense of time duration.

Zero-point Mathematical Lessons for a child:

To teach a child to count properly, abstractly, one would need to have them begin their mathematical pursuits of counting and memorizing numbers by numbering their entire hand, and it's absence (where it is hidden, covered up, or generally obscured), as the

starting point zero, the first number to be memorized, followed by the reveal of the hand which with a closed fist would be considered “one”, and then the protrusion of one finger would be considered two, and so on and so forth.

Another method would be to take a box filled with some toys, take out each toy in front of the child so they can see the math reverse engineered, and learn to understand the empty space as “zero”, the starting point, followed by adding one toy and associating it with “one”.

Sub-Cycles and Intelligent Inflammation Cycling

Sub-Cycles add further complexity within the two prime cycles; here are some creative examples:

- Pro-Inflammation Sub-Cycle A: *Angiogenesis*: Nicotine / B.F.R. Training / Deep-Tissue Massage.
- Pro-Inflammation Sub-Cycle B: *Angiogenesis*: Low Dose EtOH / B.F.R. Training / Deep-Tissue Massage.
- Pro-Inflammation Sub-Cycle C: *IL-6*: Dark Roast Coffee / No Nicotine / No EtOH / Tempo Training (Strength Training) / Hyperthermia Therapy / No Massages.
- Pro-Inflammation Sub-Cycle D: *mTOR*: GlySer / No Caffeine / No Nicotine / No EtOH / Tempo Training (Strength Training) / Hyperthermia Therapy / No Massages.
- Pro-Inflammation Sub-Cycle E: *Extreme Lipolysis*: Prolonged Fasting / No Caffeine / No Nicotine / No EtOH / AM & PM Endurance Training / Hyperthermia Therapy / No Massages.
- Pro-Inflammation Sub-Cycle F: *Extended Lipolysis*: Zero-Carb Ketogenic Diet / No Caffeine / No Nicotine / No EtOH / Endurance Training / Hyperthermia Therapy / No Massages.
- Anti-Inflammation Sub-Cycle A: *mTOR / Akt*: GlySer / Hyperthermia Therapy / No Silymarin / No Hypothermia Therapy.
- Anti-Inflammation Sub-Cycle B: *Longevity*: Silymarin / Hypothermia Therapy / Low Carb Cruciferous Diet / Protein Restriction.

Cycling between two different modes of inflammation intelligently (with forethought) is suggested, such that if you go on a Pro-Inflammation Cycle of Prolonged Fasting for numerous days to enhance muscle angiogenesis and lipolysis, you should immediately switch the following week to an Anti-Inflammation Cycle revolving around a very low carbohydrate cruciferous or raw food diet that restricts starch, sugars, sweeteners, and non-essential fatty acids to prevent the post-fast refeeding-induced weight gain that is liable to occur, or if you’ve been on extended Pro-Inflammation Cycle containing Nicotine and you begin to experience mood changes, cloudy thinking, or apathy, and

increasing the duration and intensity of your cardio does not improve your altered mental states, you can switch to an Anti-Inflammation Cycle that contains chronic amounts of L-Theanine to counteract dopaminergic dysfunction, and consume copious amounts of other antioxidants to quell neurological inflammation.

The enormous complexity of planning out supplement use is not lost to me, but this complexity is what makes experimentation with different chemicals so interesting, you should therefore not be dissuaded to think carefully as to what drugs or supplements you choose to take, rather than simply trusting the paraphrased words of a smooth talking biomedical extrapolator, including but not subjected solely to the strange author of this book.

Rapid Inflammation Cycling (R-IMC)

Rapid Inflammation Cycling will be an advanced method for promoting complete myogenesis i.e. Hypertrophy and Hyperplasia. This will be possible by the mercurial *time-sensitive* administration of ergogenics or drugs each day.

Because of the sheer complexity of ergogenic pharmacodynamics and pharmacokinetics I will not be able to create perfectly detailed R-IMC template, but I can give you example templates which may allow you, if you have a sufficiently high intelligence, to create your own R-IMC protocol.

Because efficient Hyperplasia requires extended recovery and detraining of over four days, and quite possibly even five, or six, when considering superslow training, you may end up training a muscle only once per week, and this will often cause a certain unknown level of capillary regression, do keep that in mind.

Please do not attempt R-IMC without first experimenting with classic IMCycling for over two years, and before becoming a biomedical research autodidact. It is far easier to engage in the borderline and suggested dual methods of inflammation cycling I have described up to this point.

Ascorbic Acid is one of the best Anti-Cycle supplements to use for R-IMC protocols, as it has a relatively short half-life, consider therefore experimenting with it by adding 5-10grams to a large water bottle and sipping it all day following the 72h mark post-exercise after your strength workout, especially if you have a long amount of detraining programmed, and remember, any muscle you train during this rapid anti-inflammation timespan will have its myogenic potential perturbed. This point will make it necessary to train the entire body in each workout session, or utilize ARCS.

R-IMC Example: Angiogenesis, Hyperplasia

Day One +0-Hours: Occlusion Training + Nicotine + L-Citrulline + Sildenafil > Hyperthermia Therapy.

Day Two +48-Hours: Hyperthermia Therapy.
Day Three +72-Hours: Acute Large Dose Lithium (2-4 Day Terminal Half-Life) – Chronic Betaine.
Day Four +96-Hours: Hypothermia Therapy – Chronic Ascorbic Acid / Betaine.
Day Five +120-Hours: Hypothermia Therapy – Chronic Ascorbic Acid / Betaine.
Day Six +144-Hours: Hypothermia Therapy – Chronic Ascorbic Acid / Betaine.
Day Seven +168-Hours: Lowest Load Aerobics to hypertrophy newly formed muscle tissue > Hyperthermia Therapy.

In the above template we see that we focus on stimulating exercise-induced angiogenesis early in the week, and immediately after and in the following two days we engage in hyperthermia therapy to facilitate the later stages of hypertrophy. In the following three days we attempt to promote / magnify differentiation through targeted chemical use and by reducing inflammation. Most importantly, half-life's must be taken into account for, which is why Lithium is only administered acutely and on day three, as it will continue exerting it's pro-differentiation effects for days after administration due to its long half-life, and continued use of it will surely perturb early hypertrophy, which may in the end only be of concern if your training is intense and highly damaging, but I take that as a given.

Discipline Should Come Before Success

It is important to remember that all ergogenic supplements and drugs (not including protein powders) are to be considered as additions to training, not the foundational basis of training, they will not fix your body or mind if you train improperly. Therefore, you should find a way to improve your strength, power, muscle size, muscle symmetry, or endurance naturally before you seek an easy way to the top. If you are able to continually progress in the gym with only food, protein powder, & essential nutrients, for ten years without experiencing a severe injury, or plateau, you are ready for far more advanced and expensive supplementation beyond protein powders, including eventual PED use. Although it is probable that you have not been able to continually enhance muscle size and / or function through exercise, and that you daydream of gaining access to anabolic steroids, to expedite size or performance gains, and though it be true that you are likely to overcome your physical plateaus rapidly following PED initiation, it is also true that by attempting to or succeeding in bypassing solving the extremely complex equation of continuing to facilitate natural (natural = no anabolic steroids) muscle growth or muscle conditioning improvements while you are young and healthy, you display intellectual weakness, and deserve no respect from other lifters. But for those of you who solved the

equation by experimenting with changes to your diet, exercise type, repetition tempo, repetition volume, rest period time, frequency of exercise sessions, and detraining times—you are ready to experiment with any "illegal" substance your heart desires, for you have mastered your natural born physiology, and are ready for the next step in physical evolution, if you so choose.

In a perfect world, any serious lifter or athlete, any man or woman, will pursue unenhanced lifting until they turn thirty or forty years old, which is the point in time where their natural hormone production will begin to decrease, as this will result in the greatest amount of accrued training experience, supplementation, and dietary wisdom, all of which can be applied intelligently to higher intensity (enhanced) exercise and more demanding diet protocols, rather than taking the easy way to the top of pyramid by abusing the strongest myogenic drugs on the planet at an early age, only to perish from cardiovascular complications and have your death be rationalized by fitness influencers as a "genetic heart condition". There is reason why most bodybuilders and powerlifters who go off gear look horrible, and it's not merely due to the loss in muscle, but its due to the loss in their confidence, and the unsustainability of their workout protocols (high volume, high load, high frequency), they are unable to adapt to the change of delayed wound healing, and exercise moderation.

It is sad that the fitness community is plagued by foolish young men who have been given access to steroids at too young of an age, who toss around heavy weight in the gym confidently, as if they earned their strength, those of whom have weak minds, for they never learned patience, that of which can only be mastered through years of natural lifting, and although they have strong and large muscles, they will atrophy both intellectually and physically when they go off their chosen drug cycle.

The path to success should not be rushed, as is often the case, we assume in our youth that if we do one more set, or lift five more pounds, we will be content. The truth is that when one goal is reached, another comes into the periphery, the mountain peak is always in our view, but never truly reached. For those who rush upwards without introspection and a keen knowledge of the body's abilities, they end up slipping and falling down the mountain, coming to rest at a point that is lower than when they started.

Although aging naturally results in a progressive loss in muscle mass, this does not mean that a human body cannot continue to progress in the gym even into old age as there will always be novel myogenic modalities and myogenic supplements to experiment with if you follow the fitness trends, and keep up to date with the newest scientific research. If you are not a competitor of a specific sport, there is no reason to rush your progress in the gym, for if patience is combined with scientific and kinesiological wisdom, senescence becomes far less frightening.

Now I know some of you are thinking of and prepared to offer a logical rebuttal of what you have just read by bringing up the issue of Muscle Memory, as it is true that the myonuclei density we accrue during youth, and during steroid use, are near-permanent muscle memory signatures that allow our muscles to return to their highest functioning

state after deloading, detraining, or even after withdrawing from steroids, and this would argue in favor of engaging in the most strenuous and high frequency exercise sessions in youth, to accrue the greatest myonuclei density, but this accrued muscle memory is useless if you tear or rupture any specific component of your musculoskeletal system due to overtraining, and eventually develop chronic pain, or permanent muscle weakness during later life due to incompetent or cowardly and greedy orthopedic surgeons who run rampant in our country, who prefer to profit from cortisone injections which decay muscle, joint, & tendon indiscriminately, rather than entertain as the first option, surgery, or experimental biomedical therapy.

The Question of Motivation

Many readers of this book may not be as exercise-inclined as I am, or as other readers, they may have trouble motivating themselves to get up in the morning to exercise, or go to gym after work, and in these situations it may be necessary to hire a personal trainer, or go to the gym with a friend, or family member, for even if you only walk on a treadmill for only thirty minutes, you are accomplishing something in your life, and you are on the right path to develop an interest and obsession in fitness.

It is not uncommon that people over a certain age, who are not, or who cannot afford hormone replacement therapy, lack the physiological drives necessary to propel them towards physical exertion, and this is where exercise classes come into play. Going to the gym with an unfit family member is a good starting point to reach your designated state of being, but it is far from enough to stimulate your interest in exercise. Exercise classes are the next step towards physical rejuvenation, no matter how aged, sick, or weak you are, as there are so many to choose from, whether it be Spin Class, Pilates, Yoga, or Swim Aerobics, you can experiment with all that are available to you, and once you desensitize yourself to the embarrassment of your meager motivation or physical ineptitude, you will find peace in social fitness, as you will meet friends, friends who will inspire you to transform your life through fitness, through exertion, through sweat and lactic acid, or at least meditative physical movements.

After you have rehabilitated your psyche and become healthier, and more energized, you can begin training alone, and eventually you will become who you were destined to be, that being a highly self-sufficient creature.

Microbiome Cycling

We understand thus far that certain probiotics and foods are highly beneficial to systemic cellular health, but we also know that even dysbiosis-related microorganisms and foods are capable of enhancing carbohydrate metabolism, or promoting pro-inflammatory immune activity, and this knowledge may one day be utilized intelligently. If Kimchi, Nattō, and Kefir either promote Bacteroidetes growth, or inflammatory

immunostimulation, then it could be suggested that if an athlete, or gymgoer was to consume large amounts of these probiotic foods (dsybiotic foods?) during their most strenuous workout protocols, those that involve a very high frequency of exercise sessions, that they may grow physically stronger or more powerful through carefully changing their microbiome in favor of a pro-inflammatory microbiota makeup. No doubt this idea of mine is extremely hypothetical, and is not suggested for those with serious preexisting health conditions, but for those who are young, intelligent, successful, and physically determined, it is a very intriguing idea to play with, for short periods of time, Microbiome Cycling, of purposefully promoting a controlled dsybiotic state. If cardiovascular exercise is frequently pursued, and is performed for longer periods of time, the deleterious effects of an unhealthy gut can be partially counteracted, for a time, but obviously it is of the utmost importance that the gut be restored, or renewed, with the friendliest and safest microorganisms (Lactobacilli – Bifidobacterium) during periods of detraining, deloading, or when terminally aged. Look to Beta-Glucans as an example, they may not drastically alter our microbiome, but they do stimulate a systemic immune response if consumed in large enough quantities.

Clearly, it must be mentioned that even with the overconsumption of inflammatory fermented foods, the microbiome may not enter into a dsybiotic state, if exercise is performed at a high frequency, sleep is maintained, and stress is controlled.

It is my hypothesis, and I say this after having read over 100,000 research article abstracts (which in reality is not very impressive), that it is possible to temper, to control inflammation, simply through exercise. Many people understand that high intensity training, and destructive physical training such as the use of Extreme Tempos results in release of chronic amounts of both ROS and inflammatory factors, but many more do not understand that low intensity training, below the threshold of lactic acid, specifically aerobics, and Endurance Training at very low intensities and with low effort will quell or mitigate physiological inflammation. Interluekin-6 is consistently reported to cause myopathy, and be deleterious to muscle tissue if overexpressed or chronically expressed, but what happens when a muscle is activated not acutely, but chronically, when the muscles are flooded with blood for long periods of time, can it really be said that IL-6 is as dangerous as many researchers purport it to be? There are many successful cardiovascular athletes who overconsume simple carbohydrates, and are more than likely to harbor higher populations of “bad bacteria” in their gut, but because of their choice of exercise, it’s impressive volume, and its systemic antioxidant effects, they age gracefully, but for those who feed their inflammatory intestinal brethren, through bad dieting, without utilizing Endurance Training, they clearly suffer in later life through pathological inflammation.

I know that some of the strongest and most powerful people on this planet possess microbiomes that will eventually result in their accelerated physiological aging, and premature death, but how much physical improvement can be achieved by promoting the growth of pathological microorganisms in our gut? Only time and research will tell.

Metabolic Cycling

There is a natural wisdom to skipping breakfast, working out on an empty stomach in the morning, and training hard in the evening, followed by eating a macronutrient rich meal before bed. This way of living is the ancient hunter-gatherer way, mTOR & AMPK cycling; Where in the earliest hours of the day, AMPK expression is promoted, and in the latest hours of the day, mTOR expression is promoted. Although I am unsure as to how this would affect myogenesis, beyond amino acid availability (protein synthesis), it does make sense from a physiological and cognitive standpoint, to promote mitochondrial bioenergetics in the early hours of the day, when we perform the most demanding cognitive tasks, followed by promoting a pro-myogenic, regenerative state during the evening hours leading up to sleep.

The most natural Metabolic Cycle can be achieved through the use of Green Tea and EGCG in the morning, while performing cardio in a fasted state, followed by the consumption of two or three Ketogenic meals (MCT oil only), whereas in the evening hours, carbohydrates and longer chain fats would be incorporated into your meals, preparing the body for a greater anabolic response (beyond mTOR), which it will need following your evening resistance training.

The misinterpretation and misuse of Inflammation Cycling

When Inflammation Cycling gains popularity, either from this work or similar works inspired by this work, it is highly possible that there will be a lack of nuanced complexity detailed by the individuals who claim to have mastered this concept.

Increasing inflammation through precise supplementation or lack thereof will never rival the anabolic effects of steroids, whereas it is possible that injected stem cells with cytokines or growth factors may surpass anabolic steroid myogenic efficacy to form the next generation of super muscular athletes. However, it is morally wrong to suggest inflammation be facilitated in individuals who suffer from lower classical intelligences, or mental illnesses, as they are in desperate need of antioxidants to enhance their cognitive health and abilities. These new inflammation gurus will tell teenagers and adults without a college education who work low paying trivial jobs to avoid taking all vitamins, minerals, and antioxidants. Unfortunately, this will do them no favors towards promoting the growth of their careers or lives, for their brains are far more important than their muscles, and most importantly, supplements and high end myogenic therapies will always cost money, money that could be spent more wisely, such as towards education, investments, transportation, or home purchasing.

As covered previously it is important to understand that unfettered inflammation is not good for the brain, and this can be mitigated by high frequency cardiovascular exercise, which is something most gym goers sadly despise. It may be true that certain inflammation factors promote memory processes, but it does not mean that inflammation should be used solely for the purposes of enhancing cognition, except for during

infrequent creative or intellectual ventures, as inflammation is a double-edged sword of growth and decay.

It is true that in healthy individuals, the promotion of inflammation and of angiogenesis will only bolster their intelligences and physical prowess, but these individuals are most likely already successful career-wise. Remember that if you lack wealth, you lack a powerful unconsciously expressed nootropic, and that means that your only option to enhance cognition is chronic cardiovascular exercise, phytochemicals, and essential nutrients. It is better to use copious amounts of essential nutrients and phytochemicals and engage in primarily cardiovascular exercise while delaying your myogenic potential if you can boost your intelligence through the promotion of neurogenesis, and neuritogenesis, or halt degenerative neurological processes, and utilize your new intelligence to enrich your life. One must plan for the future, and a future devoid of vitamins & phytochemicals is a dangerous game to play, and no amount of easily accessible (not biomedical) Pro-Inflammatory supplements or modalities will provide one with the same results as steroid use, there is no point in pursuing myogenic anabolism in youth when you can pursue cardiovascular and antioxidant-induced neurogenesis to facilitate optimal cognition and sublimation abilities, ultimately leading to the accrual of a sufficient amount of, as Robert Anton Wilson called it, “Bio-survival tickets”, that can be used to live a comfortable low stress life. Of course, in the cases wherein an individual earns a sufficient income by working a respectable job, neurotoxicity is of no concern until old age comes, which if not planned for through forethought and counteracted through biomedical wisdom will create chaos in a person’s final years, through the unintended progression of cognitive decline from dementia, sarcopenia, or cancer metastasis.

Am I too a Medical Charlatan? + The Future of IMC

Although it may appear that I am confident in my medical wisdom, I have attempted to preface most of my ideas with a “in my opinion”, or “in my hypothesis” warning, even if I am supremely confident in some of my novel reasoning. I have no medical degree behind me, no descriptor before or after my name to assure the intellectual respect of my readers is a given. I have mentioned in the Forward that I do not claim to be intelligent—to be capable of breezing through college courses and memorizing vast amounts of information, I am in fact far more creative than analytical, although the opposite may appear true at times. The summarizations to most of the research articles I have provided are often quite simplistic and not eye-opening, they are not meant to confuse the reader into thinking I am a supremely skilled analyst, even if I consider my pattern recognition skills to be impressive.

In the future there will many deviations from my brainchild IMC and its original nomenclature, such as I predict “Inflammation Modes”, “Inflammation Oscillating”, “Inflammation Pulsating”, et cetera, and in time there will be people far more skilled at understanding this complex multifaceted science than I, but these inflammation experts

should *never* be conventional or Alternative Medicine Doctors, for their brains have been filled with far too many pieces of *irrelevant knowledge in school to grasp the complexities and necessities of both forms of inflammation, and they will be too mentally-analytically bound by to see the intertwining and hypercomplex patterns of inflammatory processes. Only autodidacts should be given the respect and honor of Inflammation Consultation, as through self-study comes creativity, which leads to introspection, and finally innovation. Unfortunately, many of the autodidacts and college educated inflammation experts will be too busy going on podcasts and making YouTube videos to actually help people, individually, & thoughtfully, as they pursue clickbait titles and overuse inflammatory buzzwords to attain fame and wealth. This form of advertising will have the benefit of promoting IMC sciences to the general public, but it will also confuse many people into believing inflammation is always a force for good, contrary to the popular social media natural medicine edicts of our century.

I will clarify that it is not my goal to create a divide between those who live in the comfort of the anti-inflammatory green milieu and those who live in the fires of the inflammatory blood red milieu, but that does not mean that these two communities should not argue, for argument and debate will only help to refine—to further clarify IMC sciences, and help us all to better understand what, when, and to what degree these scientific trends are effective, and when and how they become dangerous.
To finish my train of thought, even though I consider myself the father of this new scientific trend, I do not find it necessary to proliferate my work to every reach of the internet by spamming my name and IMC everywhere, as those who seek knowledge shall find it, and I know that a select few readers will undertake their own serious studies on this subject, and enact positive change in the world by starting their own inflammation-based companies, pursuing consultation services, inventing novel exercise equipment, and by developing their own supplements. This fact does not make me jealous, for even if IMC fails to earn me enough monetary profit to make a living, while other Inflammation Science books, teachers, or dopaminergic hijacking YouTubers profit gratuitously, I will be content to move towards another scientific venture, for I have so many ideas that need catalyzation and execution, and even if those fail I am not against working a normal job, confined to a life of obscurity, for I have created through compilation, elaboration, & innovation something I am proud of, and this makes me happy. But there is an as of yet unresolved question—a final thought I have for you…

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*irrelevant = knowledge learned that is contrary to IMC sciences

Questions & Answers

Q: There are too many supplements to choose from on the Anti-Cycle, which should I purchase if I am on a strict budget?
A: Consider starting with Aminos (Whey Isolate), & Essential Fats (Hempseed oil or Grapeseed oil, & Chia Seed oil or Flaxseed oil), followed by the Vitamins; A(+B-Carotene)-B(1-12)-C-D-E-K.

Q: Is it possible to combine occlusion training with an Anti-Cycle?
A: I know there are benefits to hypoxia training, regardless of angiogenesis, but I am relatively certain occlusion training results in blood vessel damage, and therefore it is best to keep it within the Pro-Cycle. This does not mean that post-exercise angiogenesis is not also capable of being impeded by excessive inflammation, such as in smokers, or chronically inflamed individuals, but it does not make logical sense to me to engage in any form of hypoxia training while consuming ergogenics that inhibit or suppress angiogenesis.

Q: My doctor told me to take Ibuprofen-Aspirin-Acetaminophen or any other NSAID after I injured my muscles/tendons, I thought quelling inflammation promotes wound healing?
A: No, inhibiting Cyclooxygenase-2 during the early stages (weeks) of a severe injury will cause muscle fibrosis and aberrant collagen bundle formation in tendons, predisposing you to further injury. Although there is some conflicting research on this topic, I speak from experience, and regarding tendon injuries, unless you suppress inflammation while simultaneously stimulating collagen synthesis, such as through the use of large concentration of Ascorbic Acid, you will only weaken yourself through the use of over-the-counter junk medicine.

Q: I am on the Pro-Cycle, I am experiencing daytime sleepiness, and I feel unwell, what should I do?
A: Firstly, how often are performing your steady-state cardio? It should be five or more days per week. Secondly, if your cardio is performed at an optimal frequency, you should experiment by increasing your steady-state cardio duration by thirty minutes, and you should attempt to go to sleep earlier each night by restricting your blue light exposure before bed. Finally, if these changes fail to improve your mental health, try the MOMENT Workout Protocol, or switch to an Anti-Cycle.

Q: I am not losing any fat on the ketogenic diet, why is this?
A: If you are truly on the zero-carbohydrate ketogenic diet, and you have reached a plateau or seen no results from the start, I assume it is because you are consuming far too much Palmitic acid / Oleic acid, and to a lesser degree Linoleic acid, therefore remove

from your diet fatty meat, cheese, & lower your consumption of vegetable or seed oils. If your diet is not the culprit of your body's failure to engage the lipolytic program, it may be psychological stress. If stress is the causal factor, there is no point in dieting until your psychological issues are resolved, or you are able to inhibit cortisol release. Regardless of which of the two aforementioned causes (Diet / Stress) are negatively impacting your metabolism, the primordial brute force method to breakthrough lipolytic plateaus is through endurance training, which I define as steady-state cardio lasting over sixty minutes. Do try the SSCD or Lipolysis Endurance Protocols.

Q: My biceps never grow from training, is it bad genetics?
A: No, it is not *only* your genetics. As you are most likely *not* on anabolic steroids, you are liable to chronically overtrain your biceps, which you do so with back training every week. Find new ways to train your back such as with rear delt fly variations and allow your biceps to rest from high loads for a year while training them with very low loads only (occlusion training / lactic acid training / 1LB Hike & Curl). If you are too embarrassed to be seen curling 1-5LB Dumbbells, you are too immature to make progress.

Q: My calves never grow from training, is it bad genetics?
A: No, it is not *only* your genetics. The most impressive part of the gastrocnemius is the soleus, and this muscle can only be developed by high volume (slow twitch) exercise. Of note, I find that most individuals with small calves wear very narrow shoes, thereby restricting toe flexion, and ankle flexibility, it may be necessary then to buy either toe shoes or 4E width shoes to exercise their calves in.
The three main methods I suggest for growing calve muscles are:

1. Walking on uneven surfaces such as on grass, or a hiking trail, to near failure (2+ Hours) once a week, with a weight vest if you're lean, allowing a minimum of 96 hours of recovery between training them again, and avoiding high load resistance training until an adequate level of hypertrophy is achieved.
2. Deep-Tissue Massage (Take a rolling pin and have a strong friend or masseuse use very high pressure to intensely massage your calves immediately after a workout).

Q: Why can't I sleep soundly, even after an intense workout?
A: Eliminate caffeine from your routine and find another stimulant. It may also be probable you have not consumed enough protein (glycine) before bed.

Q: If low dose alcohol, nicotine, & oleic acid either decrease or interfere with IL-6 release, why would you add them to the Pro-Cycle when IL-6 is vital for early muscle regeneration?
A: The Pro-Inflammation Cycle is focused on muscle & brain angiogenesis, to enhance resting cellular oxygenation, the stem cell pool, and facilitate future performance, but you

should clearly *remove* these chemicals from your routine if you are on a strength protocol, such as the 15P Protocol, or cycle between them, such as one week of B.F.R. Training and any of the aforementioned supplements, and one week of high load resistance training without them.

Q: I cannot afford supplements or good food, what are my options for enhancing muscle growth?
A: Tourniquets are not expensive on Amazon.

Q: What happens if I train a muscle with high loads within the Early Hypertrophy period?
A: You will lose more muscle tissue than normal and may experience transient gains in absolute power and strength due to enhanced neuromuscular junction growth or activity, but this is not sustainable for long periods of time, especially not if you are not on anabolic steroids. [See: Overtraining]

Q: Is the Westside Method good?
A: I do not like Louie Simmons for two reasons, firstly because he was an uptight psycho who pushed his athletes through constant overtraining into debilitating injuries, and was an abusive individual, and also because (it is my opinion) he rebranded Fred Hatfield's Soviet System-inspired Five-Ten-Five Program to form the Westside Method without adequate reference nor reverence to Hatfield. See: "Repetition Method" i.e., Hatfield's Strength, Speedwork i.e., Hatfield's Compensatory Acceleration, "General Physical Preparedness" i.e., the Foundation (A quote about GPP from Louie reads: "By doing the right amount of small workouts for strength, endurance, and prehab, you can eliminate rehab as well as soreness and a *lagging muscle group*.").[539.6][539.7][539.7.1]

Q: I have noticed that through using calipers and measuring tape I am not gaining any muscle, why is this so?
A: If you are unable to add muscle you are either overtraining with high loads, training too frequently, or lack a sufficient stem cell pool (low testosterone, low inflammation), consider firstly incorporating deloading after your heaviest workouts, second there is LAT, third is Hyperthermia Therapy, and fourth is B.F.R. Training.

Q: How can I quell sweet cravings on my diet without the use of drugs?
A: Increasing your lean protein intake is the clear answer.

Q: Why does deep tissue massage need to be painful to work effectively?
A: To penetrate the muscles great pressure must be applied, which equates to greater pain, receiving a light touch will do nothing for you. This guidance also applies to massage-induced lymph node drainage. If you don't have the necessary expendable

income to pay for weekly massage therapy, you can learn from Ronnie Coleman and rub your tight or sore pectoral, or other upper body muscle, on a hard rounded corner of an exercise machine, or you can have a friend or family member quickly, and with great pressure, elbow massage your sore or injured muscle after a workout. Foam rolling will sadly do nothing for you.

Q: I have no time for efficient warmups before my programmed exercise sessions, what should I do?
A: In terms of cardio protocols involving adjustable resistance machines, you can warmup quite easily by gradually increasing the resistance levels over time, but you should still never cease performing resistance training warmups, with what may seem like innumerable variations in exercise form and type. Scheduling one day a week, such as a Saturday, or Sunday, to train your entire body with IMC Warmups methodology, is suggested, even if it results in a low level of overtraining, and this is one way to get around exercise time restrictions, especially regarding Endurance Training.

Q: Always lifting with a belt or using straps is smart, correct?
A: Just because the use of a super tight lifting belt or straps will add 5%+ to your max lifts does not make it appropriate for use during your *main* working sets, they (like partial ROM exercises) give you an illusion of absolute strength. By gaining natural (core muscle) and forearm strength through lifting *truly* raw you will be much more powerful than your contemporaries when you do finally add equipment. This does not mean I am suggesting you powerlift with no equipment; I am referring primarily to high volume strength training.

Q: I usually stretch my shoulders before a press workout with a wonky stick or swing around a weighted club and do crunches… that is a warmup, correct?
A: Negative.

Q: I have an addiction to lifting high loads, how do I alleviate this?
A: Create two music playlists; one calming (low tempo, happy) playlist for low load workouts, one stimulating (high tempo, emotional, aggressive) playlist for high load workouts, and rewire your brain to associate lactic acid pain and high repetitions with pleasure and stress relief, so that lifting light weight becomes in a way, cathartic.

Q: I have no appetite, and I am unable to consume enough food to grow, what are my options?
A: It turns out that the consumption of Carbonated Beverages promotes Ghrelin release[539.8], which is a hormone that stimulates hunger. I'd never suggest one to consume generic soda made with high fructose corn syrup, but you can try buying and using a Soda Stream or some similar device with some Bubly brand flavor concentrates,

which are sweetener-free, and make your own healthier version of soda to be consumed alongside each meal or before each meal. There is also the option to experiment with Growth Hormone Releasing Peptides which stimulate Ghrelin release.

Q: Do you offer consultation services?
A: Yes, please visit inflammationcycling.com.

Q: Have you not discussed the power of self-sufficiency, of "auto-didactism", why then offer consultation services?
A: Although most individuals will find this work sufficiently dense to enact change in their lives, a certain small subset of individuals who do not the possess the time, or technological skill to research, correlate, & innovate, may require assistance, and for them I am available for hire.

Q: Why would you include any reference to Freud in a book on biomedical sciences?
A: Aside from his hidden contribution to mechanical neuroscience in his Project, because many find his work to be *inflammatory*, similarly to ROS, I consider his work capable of stimulating an intellectual form of mitohormesis. Furthermore, considering excessive cortical excitation causes excitotoxicity and inflammation-release in the brain through either pyroptosis or necroptosis, the human sexual libido is directly linked to neuronal cell death and inflammation, if you consider this ridiculous you have never studied the long term psychological effects of childhood sexual abuse.

Q: If nearly every potent phytochemical exerts an anticancer effect, why are we still searching for a cure for cancer?
A: Money is like ATP, and cancer is like a megacorporation which seeks growth at any and all cost. The automated processes of corporations that allow them to grow unimpeded is to the detriment of mankind. Does this mean we need more stringent Governmental regulations? No, it means we need an informed public to choose more carefully where their donations go.

Q: I love cheese, but I wish to avoid Palmitic acid, what do I do?
A: Kroger stores sell Skim-Milk Mozzarella, which for the time being is the only low fat cheese of which I am aware of that is sold across the USA. I am certain in the coming years, as this devilish fatty acid becomes well known, we will have greater access to low fat cheeses and junk foods.

Q: I have no experience in meal preparation, or strict dieting, what do I do?
A: Purchase a Microscale, and refer to my guide on the following page.

1. The first step is planning an *ideal diet*, a diet that you would consider necessary to follow to become a professional anabolic athlete, such as a bodybuilder, a diet composed of impressively large amounts of protein, and this means figuring out what you would like your total daily protein intake to be, say 200g, 300g, or 400g.
2. The second step is to decide how many meals you could squeeze into a day, more is better, so we could decide between five, six, or seven meals.
3. The third step involves reading the nutrient label of your store bought meat, let's say Chicken Breasts, which will often give you a ratio of something like 112g Chicken / 25g Protein. With this ratio, you can calculate, alone, or with ChatGPT, the total grams of chicken you'll need to prepare each day to make enough for multiple equally portioned meals, meals which when combined reach your daily protein goal.
4. The fourth step involves deciding what vegetables, grains, or legumes to add to each meal, and in what concentration, two cups of either is usually appropriate.
5. The fifth and final step involves deciding exactly what vegetable or seed oils and how much of these oils to add to each meal, obviously if your meals are going to be carbohydrate-rich, you should be weary to overconsume fatty acids.
6. The sixth step is the most important, and optional, as you may not have the stomach, time, or money to eat more than two-three meals a day, because you have created an algorithm of macronutrient intake, you can easily use the food math you have just prepared to properly remove the extra meals you planned for in your "ideal diet", and can easily reach the equation for two, or three properly planned and balanced meals you can eat each day, until the point in time comes where you have greater free time, money, or *anabolic desire* to eat at a super high frequency. (Note: Because meat generally loses water concentration during cooking, the post-cooking weight of your meat will be decreased, even if the protein content remains the same, you should therefore not go by microscale post-cooking to portion out your meat into meals, but by eye alone, to ensure a more balanced distribution.

Q: Could you give me more instructions for steam cooking frozen cruciferous vegetables in the microwave?
A: If you purchase an 8-11 cup microwave safe glass food storage container, *with a microwave-safe plastic lid* (consider Pyrex), fill it completely with frozen cruciferous vegetables, close the lid on only three corners of the container, thus allowing only a small amount of steam to escape during cooking, the cooking time will range from 7-9 minutes, but after the timer goes off, you must allow the vegetables to continue steam cooking for another 7-9 minutes, before opening the lid, and portioning out or serving.

Q: Why did you not include more leafy greens under the Vegetable Juicing section?

A: I do not believe in juicing every green leafy vegetable in existence, as many are merely sources of B-Vitamins and minerals.

Q: What Car Polisher do you suggest for Local Vibration Therapy?
A: I personally use the WEN 6010 6-Inch Random Orbital Waxer/Polisher. Remember not to place this car polisher near your neck or you may damage your hearing cells, and do understand that inexpensive Car Polishers are the very best Vibration Therapy Devices, do not be fooled by other companies' inferior products.

Q: Is it possible to reach a point of muscle conditioning where blood vessel density has reached its threshold?
A: I believe it is possible, and if you find your strength-endurance to reach a point to where your chosen light weight workouts become too easy, you can always switch to a high load ET:SS protocol for a short period of time to put your impressive muscle capillarity and predicted increased pericyte release to good use for the promotion of maximized myogenesis. Hypothetically, if a blood vessel limit has been reached within skeletal muscle, new skeletal muscle must be grown to allow more room for blood vessels, therefore it makes sense to cycle between Angiogenic and Myogenic phases.

Q: How do I know you were the first one to hypothesize and elaborate on IMC?
A: I have copyrighted every draft of this work throughout the years as concrete proof of my ingenuity.

Q: Why do you apparently hold such disdain for the medical community?
A: I actually respect most medical specialists, but I do not treat them as my betters. They are fallible, and human, just as we are, and should be judged accordingly. The God-complex must be dismantled if we are to exist in a society that fosters the truest forms of intelligence, truth, compassion, creativity, and most importantly, modesty.

Q: Why have you included metapsychology, hypothesis, allusions to intelligent design, & other opinionated material in this book?
A: This book is an extension of myself, of the inner workings of my mind, yet nothing I have said thus far has breached the lens of scientism. Hypotheses & contrarianism are the starting points of all inquisitive thought.

Q: Why include research on the oral use of Cineole if it is relatively toxic?
A: Cineole is a future therapeutic to cure or treat, in my humble opinion, a nearly innumerable number of health conditions, and in very low concentrations it is extremely safe, and because of this it is in my opinion that it is the closest phytochemical, aside from Quercetin, to a true panacea.

Q: Why are some references missing or disorganized?
A: Certain studies have been omitted or rearranged during revision, and because I self-published this book, and had no access to a professional editor, a little Ordered Chaos is acceptable in the References section in my opinion.

Q: Didn't you just copy and paste research articles in this book, isn't that lazy?
A: Is paraphrasing alone any better? I think not, as I let the researchers speak directly. Furthermore, it is not my goal to teach you, the reader, about every applied human science, as these sciences confuse even me. Instead, it is my goal to give you the spark of knowledge that will ignite your own interest in these fields of study. A majority of these studies have existed in the ether, hidden beneath the veneer of the near-infinite technocratic depository that is PubMed. It is essential that you learn to comprehend research articles, rather than be beholden to breakthrough applied medicine research podcasters and youtubers who *paraphrase without reference*.

Future Directions

1. Low Load – Light weight training will gain popularity (or so I hope for the sake of those with injuries, obesity, and muscle weakness).
2. Anabolic steroids will steadily lose popularity as Pro-Inflammatory myogenic methods and chemicals become a new trend, although their safety will come into question. You will begin to see novel injectable forms of long acting COX2, TNF-a, and VEGF used by athletes & bodybuilders immediately post-workout resulting in noticeable gains in muscle size and performance, which will require new modes of detection in competitive sports.
3. LED Light Therapy rooms or chamber will replace Infrared Saunas.
4. The biggest and most impressive gymgoers will be using the lightest weights, while the strongest and most powerful will be using the slowest tempos.
5. Protein powders and bars will be sweetened with GlySer, replacing toxic synthetic sweeteners.
6. Musculoskeletal injuries, although still common, will be treated properly by doctors, who have for far too many years peddled or suggested the use of NSAID's, which have without question directly caused reinjury. Instead, they will strongly advise against inhibiting inflammation.
7. Fructose will be shunned in first world countries, and saved for consumption by impoverished and underweight individuals, which is its clear purpose of creation (to enhance adipogenesis).
8. TALM's will be formulated and sold over-the-counter at many grocery & supplements stores,
9. Alcoholic drinks will continue to decrease in potency, paralleling a decrease in global tendon ruptures.
10. Professional BFR Cuffs or Tourniquets will be found in every gymgoers bag.
11. The Prone Row will be considered the fourth compound lift in powerlifting competitions.
12. One day we will have access to massive vibration clamps that will encompass our entire bodies, or at the very least the arms, or legs.
13. LED diodes, nanosized, will be implanted into the body to alter or accelerate cellular processes, such as angiogenesis, especially in the brain, for fast neurological recovery from various brain insults.
14. As people begin to teach themselves complex applied medical sciences, they will gain the confidence necessary to question their doctors, and fight for their rights for the best care, ranging from drug to medical intervention choice.

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I would like to firstly thank my dear **Mother**; you have both inspired and supported my biochemical obsessions for my entire life.

Secondly is **Jesus Christ**, the conduit of my forgiveness & the catalyst of my life.

Thirdly is **Sigmund Freud**, the harsh but equitable fleshly father I never had.

Fourthly are all the **Research Scientists** who have provided me & continue to provide me with the pieces to the puzzle of my physical environment. I have displayed your logic in its original form, with references unobscured by my own Ego.

<><><>

- Skin / Joint Keyword Recommendations:
  [Collagen] [Wrinkle] [Skin Fold] [Photoaging] [Elastase] [Arthritis] [Synovial].

- Aging / Immunological Keyword Recommendations:
  [Senescence] [Immunosenescence] [Immunity] [Apoptosis] [Mitohormesis] [Autophagy +- Excessive] [Natural Killer cell] [DNA damage] [Chromosome Damage] [Lymphocyte] [Lymphatic] [Lymph].

3. Find three-twenty different research articles relating to the same subject matter and compare them, looking for discrepancies in research such as flaws in study design, potential bias, or dosage / concentration differences, to ascertain a clearer picture of the pharmacodynamics or therapeutic effects.

4. Example search: “Quercetin bDNF PubMed”, “Quercetin Adipocyte PubMed”, “Exercise Angiogenesis PubMed”.

The more specific the keywords you use during your PubMed Journeys, the more interesting research you will find, such that a search like “Exercise Angiogenesis PubMed” will yield less relevant or interesting information, as compared to a search such as “Endurance Exercise Slow Twitch Angiogenesis”. The most interesting research articles I have discovered have been found through an innumerable number of hours of web browsing, comparing dozens of research articles at one time, coupled with the creative and frequent change of my chosen keyword usage, where I always have attempted to use the most specific and complex terminologies to reach the most specific and apropos biomedical destinations.

Although time consuming, effective PubMed Journeys are not inherently difficult to achieve, but the pattern recognition required to comprehend novel information that is too complex for you to comprehend through Abstract alone, will at times be more difficult for you. Regardless of the difficulty present, it is a mistake to rely on a Large Language Model to do your research for you, or to rely on other people to summarize the research you eventually integrate into your life, as the supplement or therapeutic errors you make will be more forgiving than the errors a machine makes, or another human makes, therefore you must embrace biomedical literature comprehension self-sufficiency.

Notice: I am not affiliated with any of the companies I have mentioned in this book, nor have I been sponsored by any of them, but I am a fan of their products.

About & Epilogue

I composed this book highly caffeinated and nicotinated, because as evidenced, inflammation is important for cognition. I have always cycled between inflammatory profiles to avoid mental deterioration or psychosis from developing by having a very accurate inborn sense of drug-induced neurotoxicity, for when I begin to experience frequent memory errors, or cloudy thinking, I know it is time to take a break from recreational inflammatory chemicals, or at the very least substantially increase my cardiovascular exercise duration and / or intensity. It is wise to remember that the promotion of inflammation is always going to be a tactic for the young, who have better health resilience, and even I must relearn this wisdom from time to time.

Indeed, it is true I did not create or fund the research contained within this book, but I do consider it extremely important to bring it to the general public, and I consider myself highly capable of summarizing & correlating these studies / sciences through my creativity & ability to form connections between chemicals and processes.

Too often do I read online articles describing a certain phytochemical or ergogenic chemical as a *panacea*, and for my younger life I sought after this "prima materia", testing every medicinal plant I could find, every standardized extract, every prescription chemical available to me based on my abilities to persuade a doctor. During these many years of subjective study, I found no singular cure for my memory issues, depression, obesity, or weak muscles, and I eventually realized that just as we have comorbidities, so too must our supplements, therapies, and training types be manifold. Unfortunately, the very best myogenic, neurotrophic, or lipolytic chemicals happen to be synthesized in laboratories, hidden, and locked behind pharmacy counters, or worse, hoarded by research chemical suppliers such as MilliporeSigma. It is sad that both corporations and our overreaching governments seek to control our consumption and use of chemicals, many of which are precursors or derivatives of phytochemicals. The fact that anabolic steroids and potent lipolytic chemicals are labeled illegal for possession or distribution except for prescription proves that most governments do not want their citizens to have strong and capable bodies, especially not the elderly. We have no choice but to turn to supplement companies to escape the psychological tortures of debating the merits of Off-Label pharmaceutical use with close-minded doctors, who unlike researchers, seek only to maintain the often-fatal status quo.

When we put our faith in human beings, we lose a part of ourselves, and sometimes we lose our lives, and because of this it is then my recommendation that you (the reader) stop

believing everything your doctor tells you; Go to Wikipedia, go to PubMed, research your diagnosed medical conditions, research the mechanism of action of the drugs you are prescribed, research the side effects of those drugs, become a medical skeptic and espouse these sciences rather than fearing them for their complexity, you are capable of understanding more than you know.

There is a nearly limitless amount of research articles I know I have missed, phytochemicals I have not *yet* discovered, or myogenic processes I do not comprehend enough to include in this work. Therefore, it is to be considered an incomplete study, and only capable of being finished by the most ambitious readers.

In closing, I will remind you, the reader, that this book is to be considered a compendium of curated applied sciences, and the explanation of a new and paradoxically ancient concept of physiological existence through the facilitation of different modes, or *cycles*, of Inflammation. Because the majority of this book is exogenous research, and only a minority of it is endogenous research, hypothesis, and opinion, and because I find the information contained within this book to be potentially life changing, not spiritually of course, but physically, I have provided this book for free, for it is not my goal to profit directly from knowledge other people have discovered and or elaborated on, but I do intend on profiting from knowledge that can be applied in specific ways, knowledge that is consciously weaved into a newly recognized concept, such as with my brainchild, IMCycling, or my workout protocols. If you have found appliable value or intellectual enjoyment from the intriguing information contained within this book and wish to contact me, or if you are interested in consultation services, please visit my website inflammationcycling.com.

P.S. 1: Many commonly sold phytochemicals, recreational drugs, research chemicals, and over-the-counter ergogenic chemicals have been purposely withheld from this book due to having high POP, redundant, predictable & boring, or obviously neurotoxic pharmacodynamic effects on the brain and body, or being highly illegal. The majority of herbal extracts modulate Serotonin / Dopamine levels in the brain, or inhibit COX-2, and many recreational drugs cause excitotoxicity, such as amphetamines, and now, funnily enough, the doctor prescribed deliriant, complex neurotoxin, and beta-amyloid increaser, Ketamine[539.9][539.10][5.39.11]. Therefore, to fill this book with studies on every *boring* or outright dangerous herbal extract, every *toxic* recreational chemical, or every *popular* ergogenic chemical I am aware of would only serve as “filler” material to this work, of which would go against my hyperfocus on brevity and potency.

P.S. 2: I would like to preemptively thank anyone who references my compilatory work, or my name, through visual or written media, instead of merely presenting my intermittently expressed ideas and discoveries as their own, your integrity is admirable.

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Flawed Study Design Test Answers

Study 1:

- Age discrepancy (an elderly individual will have less strength to exert during an exercise, and therefore less systemic benefits).
- Unmonitored diet among participants.
- Unmonitored supplementation among participants.

Study 2:

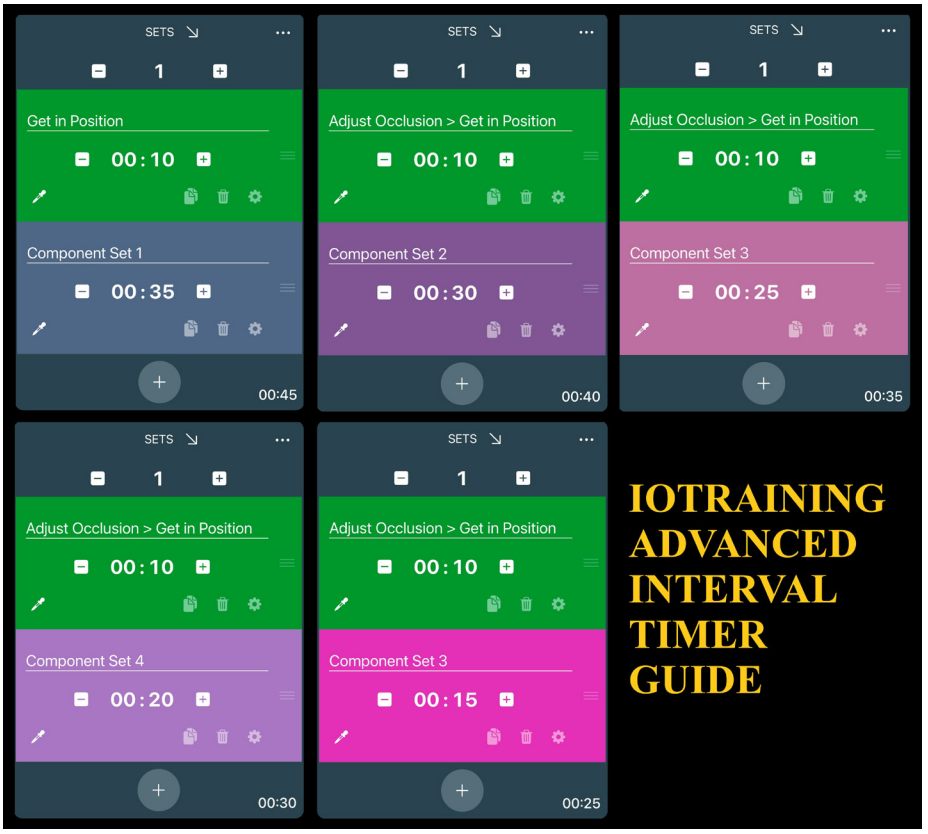
- Assuming and attributing that Green Tea polyphenols are the sole reason for a decrease in blood glucose when Caffeine, a chemical capable of interacting with blood sugar, is present in Camellia Sinensis in very high concentrations.
- Unmonitored diet among participants.
- Unrealistic dosing (Commonly sold and prepared tea will never be as strong as extracts.

Study 3:

- The species of Cinnamon used is not identified, therefore the chemical composition of the Cinnamon used is unknown, leading to serious legitimacy issues of the study.
- The supplier of the Cinnamon is relatively unknown and has no certifications proving purity and lack of contamination.

Interval Timer Guide for IOT

(Suggested for use with Interval Timer Plus App)



IMC Sciences Overview
(Extracted carefully from PubMed & *ChatGPT*)

Common Dietary Phytochemical Classifications, Examples, & Sources:

- **Anthocyanins (Anthocyanidins: Red-Purple-Blue Pigments):** Delphinidin (Blueberry), Cyanidin (Elderberry), Malvidin (Black Grape).
- **Carotenoids (Yellow-Orange-Red Pigments):** Beta-Carotene (Carrots), Lycopene (Tomato), Lutein / Zeaxanthin (Flower Petals), Capsanthin (Paprika, Cayenne, Red Pepper).
- **Phenolic Acids:** Chlorogenic Acid (Coffee), Caffeic Acid (Chokeberry), Sinapic Acid (Green Olive), Ferulic Acid (Whole Wheat), p-Coumaric Acid (Cloudberry), Vanillic Acid (Sweet Basil).
- **Flavanols:** Catechins (Cocoa, Green Tea).
- **Flavonols:** Quercetin (Elderberry, Chokeberry), Rutin (Capers), Kaempferol (Capers).
- **Flavones:** Luteolin (Chinese Celery, Oregano, Thyme), Apigenin (Parsley).
- **Tannins:** Vescalagin / Castalagin (Oak / Chestnut Bark: Liquor / Wine)
- **Lignans:** Secoisolariciresinol Diglucoside (Flax seeds).
- **Terpenes (Terpenoids):** Linalool (Cilantro), Humulene / Myrcene (Beer).
- **Phytosterols:** Beta-Sitosterol (Barley, Rice), Stigmasterol (Sunflower Seed oil).
- **Saponins:** Ginsenosides (Ginseng).
- **Glucosinates:** Glucoraphanin (Broccoli), Allyl Isothiocyanate (Wasabi, Horseradish, Mustard).
- **Alkaloids:** Caffeine (Tea, Coffee), Nicotine (Tobacco), Piperine (Black Pepper).
- **Other Pigments:** Chlorophyll (Chlorella, Spirulina), Betalains (Beet).
- **Phytoecdysteroids:** Ecdysterone (Spinach, Quinoa).

Myogenic Regulatory Factors and their Functions:

- **Myogenic Differentiation 1 (MyoD):** MyoD serves as a master regulator of skeletal muscle differentiation. It activates the expression of muscle-specific genes and initiates the conversion of precursor cells (myoblasts) into mature muscle cells (myotubes). MyoD also plays a role in muscle regeneration by promoting the activation and proliferation of satellite cells.
- **Myogenic factor 5 (Myf5):** Myf5 is involved in the early specification and commitment of multipotent mesodermal cells to the skeletal muscle lineage during

embryonic development. It activates the expression of genes necessary for muscle cell differentiation and growth, guiding myoblasts towards the skeletal muscle lineage.

- **Myogenin (MyoG):** Myogenin is essential for the terminal differentiation of myoblasts into mature muscle fibers. It regulates the expression of genes involved in myoblast fusion, sarcomere assembly, and muscle-specific protein synthesis. Myogenin also plays a role in muscle repair and regeneration by promoting the formation of new muscle fibers.
- **Myogenic Regulatory Factor 4 (MRF4 or Myf6):** MRF4 contributes to skeletal muscle development by regulating the differentiation and maturation of muscle cells. It is involved in coordinating muscle fiber type specification and the expression of genes associated with fast-twitch muscle fibers. MRF4 also participates in muscle regeneration by activating satellite cells and promoting their differentiation into new muscle cells.
- **Paired Box 7 (PAX7):** Although not considered an MRF, it is a transcription factor crucial for maintaining and activating satellite cells, playing a central role in skeletal muscle regeneration.

Mature Adipocyte Chemical Secretions (Adipokines & Adipocytokines):

- **Adiponectin:** A hormone with anti-inflammatory and insulin-sensitizing properties.
- **Leptin:** A hormone that regulates appetite and energy expenditure.
- **Resistin:** Implicated in insulin resistance and inflammation.
- **Tumor Necrosis Factor-alpha (TNF-alpha):** A pro-inflammatory cytokine.
- **Interleukin-6 (IL-6):** A cytokine with both pro- and anti-inflammatory effects.
- **Plasminogen Activator Inhibitor-1 (PAI-1):** Regulates fibrinolysis and thrombosis.
- **Retinol-binding Protein 4 (RBP4):** Involved in insulin resistance and metabolism.
- **Visfatin:** Implicated in glucose metabolism and inflammation.
- **Angiotensinogen:** Precursor to angiotensin, involved in blood pressure regulation.
- **Chemerin:** Associated with adipogenesis and inflammation.
- **Omentin:** May have anti-inflammatory and insulin-sensitizing effects.
- **Vaspin:** May play a role in insulin sensitivity and obesity.
- **Adipsin:** Involved in complement activation and adipogenesis.
- **Lipocalin-2:** Associated with obesity-related inflammation and insulin resistance.
- **FGF-21 (Fibroblast Growth Factor 21):** Implicated in metabolic regulation and insulin sensitivity.
- **Natriuretic Peptides (ANP, BNP):** Involved in cardiovascular regulation and sodium balance.
- **IL-1β (Interleukin-1 beta):** Pro-inflammatory cytokine.
- **IL-8 (Interleukin-8):** Chemokine involved in inflammation.
- **IL-10 (Interleukin-10):** Anti-inflammatory cytokine.

Reactive Oxygen Species (Free Radicals) and their effects in high or chronic concentrations:

- **Hydroxyl radical (•OH):** Causes damage to lipids, proteins, and DNA, leading to cell injury and aging.
- **Superoxide radical (•O2-):** Impairs cellular function, contributes to inflammation, and damages DNA.
- **Nitric oxide radical (•NO):** Regulates blood pressure, neurotransmission, and immune responses; at high concentrations, can contribute to oxidative stress and tissue damage.
- **Singlet Oxygen ($^1O2$) :** Singlet oxygen is formed when molecular oxygen absorbs energy, often from light or certain chemical reactions. Its high reactivity causes it to oxidize biological molecules, leading to cellular damage, oxidative stress, and potential dysfunction or death.
- **Peroxyl radical (•OOH):** Initiates lipid peroxidation, damaging cell membranes and contributing to aging and disease.
- **Alkoxyl radical (•OR):** Causes oxidative damage to lipids and proteins, contributing to aging and disease.
- **Carbon-centered radical (•CR3):** Formed during lipid peroxidation, contributes to cellular damage and inflammation.
- **Nitroxyl radical (•NO2):** A component of nitrogen dioxide, a major air pollutant that can damage lung tissue and exacerbate respiratory conditions.
- **Thiyl radical (•SH):** Impairs protein function and can contribute to cellular damage and inflammation.
- **Lipid peroxyl radical (LOO•):** Initiates and propagates lipid peroxidation reactions, damaging cell membranes and contributing to disease.
- **Protein-centered radicals (•CR2):** Cause damage to proteins, disrupting cellular function and contributing to aging and disease processes.

Growth Factors and their functions:

- **Epidermal Growth Factor (EGF):** Stimulates cell growth, proliferation, and differentiation, particularly in epithelial tissues like skin.
- **Fibroblast Growth Factors (FGFs):** Promote the growth and differentiation of various cell types, including fibroblasts, endothelial cells, and neural progenitor cells, and play roles in tissue repair and regeneration.
- **Platelet-Derived Growth Factor (PDGF):** Stimulates cell proliferation and migration, particularly of mesenchymal cells such as fibroblasts and smooth muscle cells, contributing to wound healing and tissue repair.
- **Vascular Endothelial Growth Factor (VEGF):** Stimulates angiogenesis, the formation of new blood vessels from existing ones, and vasculogenesis, the formation of new blood vessels from precursor cells, promoting tissue vascularization and repair.

- **Insulin-like Growth Factors (IGFs):** Regulate cell growth, proliferation, and differentiation in various tissues, playing roles in growth and development, as well as tissue repair and metabolism.
- **Transforming Growth Factors (TGFs):** Control cell growth, differentiation, and apoptosis, regulating various cellular processes involved in development, tissue repair, and immune responses.
- **Nerve Growth Factor (NGF):** Supports the survival, growth, and differentiation of sensory and sympathetic neurons, playing roles in neuronal development, maintenance, and regeneration.
- **Brain-Derived Neurotrophic Factor (bDNF):** Promotes the survival, growth, and differentiation of neurons in the central nervous system (CNS), influencing synaptic plasticity, learning, and memory.
- **Hepatocyte Growth Factor (HGF):** Stimulates cell proliferation, migration, and morphogenesis, particularly in hepatocytes (liver cells), contributing to liver regeneration and tissue repair.

Blood cells and their functions:

- **Red blood cells (Erythrocytes):** Transport oxygen from the lungs to tissues and carry carbon dioxide back to the lungs.
- **White blood cells (Leukocytes):**
  1. **Neutrophils:** Engage in phagocytosis to ingest and destroy pathogens.
  2. **Lymphocytes:** Play a central role in the adaptive immune response, including B cells, T cells, and natural killer (NK) cells.
  3. **Monocytes**: Differentiate into macrophages or dendritic cells to phagocytose pathogens and present antigens.
  4. **Eosinophils:** Combat parasitic infections and modulate allergic responses.
  5. **Basophils:** Release histamine and other mediators involved in allergic responses and inflammation.
  6. **Platelets (Thrombocytes):** Essential for blood clotting (hemostasis) by forming clots to stop bleeding when blood vessels are injured.

The Brain, its major parts, and their functions:

Cerebrum:
- Responsible for higher cognitive functions such as thinking, memory, perception, and voluntary movement.
- Divided into two hemispheres (left and right), each controlling the opposite side of the body.

Cerebellum:
- Coordinates voluntary movements, balance, posture, and motor learning.
- Helps maintain smooth and coordinated muscle movements.

Brainstem:

- Connects the brain to the spinal cord and regulates basic life-sustaining functions such as breathing, heart rate, and blood pressure.
- Comprises the midbrain, pons, and medulla oblongata.

Diencephalon:

- Thalamus: Acts as a relay station for sensory information (except smell) traveling to the cerebral cortex.
- Hypothalamus: Regulates body temperature, hunger, thirst, sleep-wake cycles, and hormone secretion from the pituitary gland.

Limbic System:

- Involved in emotions, memory, and motivation.
- Includes structures such as the amygdala, hippocampus, and cingulate gyrus.

Basal Ganglia:

- Controls voluntary motor movements, procedural learning, and habit formation.
- Includes structures such as the caudate nucleus, putamen, and globus pallidus.

Cortex:

- The outer layer of the cerebrum, comprises gray matter.
- Responsible for higher cognitive functions such as perception, memory, language, and decision-making.
- Divided into four lobes: frontal, parietal, temporal, and occipital, each with specific functions.

Hippocampus:

- Vital for the formation and retrieval of memories.
- Plays a role in spatial navigation and learning.

Amygdala:

- Involved in processing emotions, particularly fear and aggression.
- Plays a role in emotional memory formation and response.

Pituitary Gland:

- Master gland that regulates hormone production and secretion from other endocrine glands.
- Plays a crucial role in growth, metabolism, and reproduction.

Pons:

- Acts as a bridge between the cerebellum and the rest of the brain.
- Involved in regulating sleep, breathing, and other autonomic functions.

Medulla Oblongata:

- Controls vital autonomic functions such as heartbeat, breathing, and swallowing.

- Regulates reflexes such as coughing, sneezing, and vomiting.

Midbrain:
- Involved in sensory processing, motor coordination, and arousal.
- Contains nuclei responsible for controlling eye movements and pupil dilation.

Thalamus:
- Acts as a relay station for sensory information traveling to the cerebral cortex.
- Plays a role in regulating consciousness, sleep, and alertness.

Hypothalamus:
- Regulates body temperature, hunger, thirst, sleep-wake cycles, and hormone secretion from the pituitary gland.
- Controls the autonomic nervous system and the body's response to stress.

Corpus Callosum:
- Thick band of nerve fibers that connects the two hemispheres of the cerebrum.
- Facilitates communication and coordination between the left and right sides of the brain.

Olfactory Bulb:
- Processes olfactory (smell) information received from the nasal cavity.
- Plays a role in odor detection and discrimination.

Reticular Formation:
- Extensive network of neurons located throughout the brainstem.
- Regulates arousal, attention, and consciousness.

Septum:
- Involved in emotional regulation, memory consolidation, and reward processing.
- Plays a role in social behavior and aggression.

Corpora Quadrigemina:
- Located in the midbrain, consists of four rounded elevations.
- Contains nuclei involved in visual and auditory processing.

Pineal Gland:
- Secretes melatonin, a hormone that regulates the sleep-wake cycle and circadian rhythms.
- Plays a role in seasonal and reproductive functions.

The Cornu Ammonis (CA) areas of the brain:

These are regions of the brain contained within the Hippocampus that are involved in many forms of memory, which are numbered CA1, CA2, and CA3. These CA subfields

play distinct roles in memory processing and have unique cellular and synaptic properties.

The three CA subfields and their relation to memory:

1. **CA1 Subfield:**
    - **Function**: CA1 is involved in the consolidation and retrieval of declarative memories, which are memories of facts and events. It receives inputs from the CA3 region and sends outputs to other areas of the brain, including the entorhinal cortex and neocortex.
    - **Cellular Properties:** CA1 pyramidal neurons are characterized by their extensive dendritic arborization and complex synaptic connections. They receive inputs from both the perforant path (from the entorhinal cortex) and the Schaffer collaterals (from CA3 pyramidal neurons).
    - **Relation to Memory:** Lesions or dysfunction in the CA1 region can impair the encoding and retrieval of declarative memories. Studies have shown that damage to CA1 can result in anterograde amnesia, where new memories cannot be formed, as well as retrograde amnesia, where previously formed memories are lost.
2. **CA2 Subfield:**
    - **Function:** CA2 is less well-studied compared to CA1 and CA3, but emerging research suggests that it may play a role in social memory and social behavior. It receives inputs from CA3 and sends outputs to CA1 and CA3.
    - **Cellular Properties:** CA2 neurons have unique molecular and synaptic properties that distinguish them from neurons in neighboring regions. They express specific receptors and ion channels that contribute to their functional specialization.
    - **Relation to Memory:** While less is known about the specific role of CA2 in memory processing, studies in animal models suggest that it may be involved in the recognition and processing of social cues and contexts. Dysfunction in CA2 has been implicated in social memory deficits observed in certain neuropsychiatric disorders.
3. **CA3 Subfield:**
    - **Function:** CA3 is primarily involved in pattern completion, the process by which incomplete or degraded input patterns are restored or completed to retrieve stored memories. It receives inputs from the dentate gyrus and sends outputs to CA1 and other regions of the hippocampus.
    - **Cellular Properties:** CA3 pyramidal neurons are known for their recurrent collateral connections, which form a dense network of excitatory synapses within the region. This recurrent connectivity is thought to contribute to the computational properties of CA3, including pattern completion.

- **Relation to Memory:** Lesions or dysfunction in CA3 can impair the ability to retrieve memories from partial or degraded cues, leading to deficits in pattern completion. This has been observed in animal studies and computational models of hippocampal function.

Dopamine Receptors and their behavioral functions:

- **D1 receptor:** Regulates reward, motivation, cognition, and motor control.
- **D2 receptor:** Influences reward, movement, and emotional processing; implicated in addiction and psychosis.
- **D3 receptor:** Linked to motivation, emotion, and addiction; associated with depression and schizophrenia.
- **D4 receptor:** Involved in attention, learning, and memory; associated with ADHD and schizophrenia.
- **D5 receptor:** Plays a role in cognitive processes, motivation, and synaptic plasticity.

Serotonin Receptors and their behavioral functions:

- **5-HT1A receptor:** Regulates mood, anxiety, aggression, and cognition; implicated in depression and anxiety disorders.
- **5-HT1B receptor:** Modulates mood, anxiety, and aggression; involved in addiction and impulsivity.
- **5-HT1D receptor:** Influences pain perception and migraine headaches.
- **5-HT1E receptor:** Less understood; potential role in mood regulation.
- **5-HT1F receptor:** Implicated in migraine headaches.
- **5-HT2A receptor:** Regulates mood, perception, and cognition; involved in hallucinations and psychosis.
- **5-HT2B receptor:** Linked to mood regulation, appetite, and cardiac function.
- **5-HT2C receptor:** Modulates mood, appetite, and addiction; potential target for obesity and depression treatments.
- **5-HT3 receptor:** Involved in nausea, vomiting, and anxiety.
- **5-HT4 receptor:** Influences mood, memory, and gastrointestinal motility.
- **5-HT5 receptor:** Functions not well understood.
- **5-HT6 receptor:** Associated with learning, memory, and cognitive function; potential target for Alzheimer's disease.
- **5-HT7 receptor:** Implicated in mood regulation, cognition, and sleep.

GABA Receptors and their behavioral functions:

- **GABA-A receptor:** Mediates fast inhibitory neurotransmission; regulates anxiety, sedation, and muscle relaxation.

- **GABA-B receptor:** Mediates slow inhibitory neurotransmission; influences mood, sleep, and pain perception.
- **GABA-C receptor:** Less understood; may modulate visual processing and motor control.

VEGF Receptors and their functions:

- **VEGFR-1 (Flt-1):** Involved in regulating angiogenesis, vasculogenesis, and vascular permeability.
- **VEGFR-2 (KDR/Flk-1):** Main mediator of VEGF-induced angiogenesis, promoting endothelial cell proliferation, migration, and survival.
- **VEGFR-3 (Flt-4):** Primarily associated with lymphangiogenesis, regulating lymphatic endothelial cell growth and differentiation.

Muscle Loss Terminology:

- **Sarcopenia:** Age-related loss of muscle mass, strength, and function, leading to decreased physical performance and increased frailty.
- **Atrophy:** Decrease in the size and function of a tissue or organ, such as muscle, due to factors like disuse, injury, or disease.
- **Disuse:** Reduction in muscle activity or movement, leading to loss of muscle mass and strength, typically due to immobilization, sedentary lifestyle, or prolonged bed rest.
- **Cachexia:** Chronic illness-induced muscle loss due to either inflammation or muscle atrophy factors.
- **Denervation:** When nerves that innervate muscles are damaged or severed, the affected muscles lose their neural stimulation, leading to atrophy. This can occur due to conditions such as spinal cord injury, peripheral nerve damage, or motor neuron diseases like ALS (amyotrophic lateral sclerosis).

The Scientific components of Muscle Contraction:

- **Actin:** Actin is a protein that forms thin filaments in muscle cells. It serves as the primary component of the contractile machinery in muscle fibers.
- **Myosin:** Myosin is a motor protein that comprises thick filaments in muscle cells. It contains "heads" that can bind to actin filaments and generate force during muscle contraction.
- **Filaments:** Filaments refer to the long, thread-like structures formed by the assembly of actin and myosin proteins within muscle cells. Actin and myosin filaments interact to produce muscle contraction.
- **Calcium ions:** Calcium ions play a crucial role in muscle contraction by regulating the interaction between actin and myosin. They are released from the

sarcoplasmic reticulum in response to nerve impulses, initiating muscle contraction.

- **Sarcomeres:** Sarcomeres are the basic structural and functional units of muscle contraction. They are composed of overlapping actin and myosin filaments and are responsible for the generation of force and movement in muscle fibers.
- **Sarcoplasmic reticulum:** The sarcoplasmic reticulum is a specialized organelle within muscle cells that stores and releases calcium ions. It plays a central role in regulating intracellular calcium ion concentrations and initiating muscle contraction.
- **ATP hydrolysis:** ATP hydrolysis is the process by which ATP molecules are broken down into ADP (adenosine diphosphate) and inorganic phosphate, releasing energy. This energy is utilized by myosin heads to power the movement of actin filaments during muscle contraction.
- **Myosin heavy chain (MHC):** A large protein composed of multiple subunits found in the myosin protein complex (myosin molecules) within skeletal muscle that determine muscle fiber type, often changing composition depending on exercise or lack thereof. There are four isoforms of MHC:

1. **MHC-1** (Type 1: Slow Twitch Fibers: Oxidative Fibers).
2. **MHC-II** (Type IIa: Intermediate fibers: Oxidative & Glycolytic).
3. **MHC-IIx** (Type IIx: Fast Twitch Fibers: Glycolytic Fibers).
4. **MHC-IIb** (Type IIb: Fast Twitch Fibers: Glycolytic Fibers: Faster Contraction Speed than MHC-IIx).

The chemical cascade leading to Muscle Contraction:

1. **Neuromuscular Activation:** Muscle contraction is initiated by nerve impulses traveling along motor neurons to the neuromuscular junction, where they stimulate the release of neurotransmitters, typically acetylcholine.
2. **Calcium Ion Release:** The binding of acetylcholine to receptors on the muscle cell membrane triggers the release of calcium ions (Ca^{2+}) from the sarcoplasmic reticulum, a specialized organelle within the muscle cell.
3. **Actin-Myosin Interaction:** Calcium ions bind to regulatory proteins on actin filaments, exposing binding sites for myosin heads. Myosin heads, attached to thick filaments, then bind to actin filaments, forming cross-bridges between actin and myosin.
4. **ATP Hydrolysis:** The energy required for muscle contraction is derived from the hydrolysis of adenosine triphosphate (ATP) to adenosine diphosphate (ADP) and inorganic phosphate (Pi) by the enzyme myosin ATPase. This energy is used by myosin heads to pivot and pull actin filaments towards the center of the sarcomere.
5. **Power Stroke and Sliding Filaments (Muscle Contraction):** As myosin heads pivot, they generate force and slide actin filaments past myosin filaments towards the center of the sarcomere. This shortens the sarcomere and produces muscle contraction.

6. **Relaxation (Muscle Relaxation):** When the nerve impulse ceases, calcium ions are actively pumped back into the sarcoplasmic reticulum, reducing the cytoplasmic calcium ion concentration. This causes the regulatory proteins on actin to return to their original conformation, blocking the myosin-binding sites and preventing further cross-bridge formation. The muscle returns to its original length, and relaxation occurs.

The different types of Autophagy:

1. **Microautophagy:** Direct engulfment of cytoplasmic components by lysosomes for degradation.
2. **Chaperone-Mediated Autophagy (CMA):** Degradation of specific proteins, guided by chaperones like HSC70.
3. **Mitophagy:** Selective degradation of damaged or unnecessary mitochondria.
4. **Pexophagy:** Degradation of peroxisomes, which are involved in lipid metabolism and detoxification.
5. **Ribophagy:** Degradation of ribosomes to manage cellular stress or turnover.
6. **Lipophagy:** Degradation of lipids to regulate energy homeostasis.
7. **Glycophagy:** Degradation of glycogen to maintain glucose levels during nutrient deprivation
8. **Aggrephagy:** Degradation of protein aggregates to prevent toxic accumulation.
9. **Xenophagy:** Degradation of invading microorganisms, a form of host defense.

Resistant Starch:

Resistant Starch are polysaccharides (carbohydrate molecules) that resist digestion, resulting in a lower spike in blood glucose / insulin following consumption, making them healthier choices for not only weight loss purposes, but also life extension purposes.

The four types of Resistant Starch:

1. **RS1 - Physically Resistant Starch:** This type of resistant starch is found in whole or partially milled grains, seeds, and legumes, where it is protected by cell walls or complex structures that resist digestion.
2. **RS2 - Granular Resistant Starch:** Granular resistant starch consists of starch granules that are resistant to digestion due to their crystalline structure or high amylose content.
3. **RS3 - Retrograded Starch:** RS3 is formed when starchy foods such as potatoes, rice, or pasta are cooked and then cooled. The process of cooling causes some of the starch to retrograde or recrystallize into a more resistant form.
4. **RS4 - Chemically Modified Starch:** RS4 refers to starch that has been chemically modified to resist digestion. This type of resistant starch is often added to processed

foods as a functional ingredient to increase fiber content or improve texture. There are dozens of RS4 chemicals, chemicals that promote changes to starch, and I do not believe they are necessary nor healthy for consumption, considering we have natural forms of Resistant Starch.

The food highest in each of the four types of Resistant Starch:

1. **RS1 - Physically Resistant Starch**:
    - *Foods*: Whole or partially milled grains, seeds, and legumes.
    - *Examples*: Intact whole grains (such as barley, quinoa, and brown rice), seeds (such as flaxseeds and chia seeds), legumes (such as lentils, chickpeas, and beans)
2. **RS2 - Granular Resistant Starch:**
    - *Foods*: Raw or unripe starchy vegetables and fruits
    - *Examples*: Raw potatoes, green bananas, raw plantains, raw corn, raw rice, raw legumes.
3. **RS3 - Retrograded Starch:**
    - *Foods*: Cooked starchy foods that have been cooled.
    - *Examples*: Cooked and cooled potatoes, rice, pasta, oats, bread, and corn.
4. **RS4 - Chemically Modified Starch**:
    - *Foods*: Processed foods with added resistant starches
    - *Examples*: Low-carb products, fiber-enriched foods, resistant maltodextrin, resistant starch supplements, gluten-free products.

The main layers of the Skin and their relationship to aging:

1. **Epidermis:** The epidermis is the outermost layer of the skin and acts as a barrier to protect the body from external factors such as pathogens, UV radiation, and chemicals. It is primarily composed of keratinocytes, which produce the protein keratin, as well as melanocytes, which produce melanin, the pigment responsible for skin color. The epidermis also contains Langerhans cells, which are involved in the immune response.
    - **Relation to Aging:** Aging can lead to thinning of the epidermis, which can result in increased susceptibility to injury and decreased barrier function. Additionally, aging can affect the turnover of skin cells, resulting in slower wound healing and a duller complexion. Changes in melanocyte function can lead to uneven pigmentation, such as age spots or solar lentigines.
2. **Dermis:** The dermis is the middle layer of the skin and provides structural support and elasticity. It contains various components, including collagen, elastin,

and fibroblasts, which contribute to the skin's strength, flexibility, and resilience. The dermis also contains blood vessels, lymphatic vessels, nerves, and appendages such as hair follicles and sweat glands.

- **Relation to Aging:** Aging can lead to a decrease in the production of collagen and elastin, resulting in loss of skin firmness and elasticity. This can contribute to the formation of wrinkles, sagging skin, and fine lines. Changes in blood vessel structure and function can lead to reduced blood flow and nutrient delivery to the skin, further exacerbating signs of aging.

3. **Hypodermis (Subcutaneous Tissue):** The hypodermis is the innermost layer of the skin and primarily consists of adipose tissue (fat) and connective tissue. It provides insulation, cushioning, and energy storage, as well as anchorage for the skin to underlying structures such as muscles and bones.

    - **Relation to Aging:** With age, the hypodermis may undergo changes in fat distribution, leading to loss of volume and support in certain areas of the face and body. This can contribute to the appearance of hollowed cheeks, sunken eyes, and thinning lips. Additionally, changes in connective tissue can affect the overall structure and integrity of the skin.

Receptor Dynamics:

A. Receptor:

- A receptor is a specialized protein molecule located on or within a cell. It binds to specific signaling molecules, such as hormones, neurotransmitters, or drugs.
- Receptors play a crucial role in cellular communication by transducing extracellular signals into intracellular responses, thereby regulating various biological processes.

B. Expression of a Receptor:

- Receptor expression refers to the synthesis or production of receptor proteins by a cell.
- Receptor proteins = receptors, therefore increased receptor expression means the process of forming new receptors.
- Cells can regulate the expression of receptors based on various factors, including developmental stage, physiological conditions, and external stimuli.
- Higher receptor expression can increase the cell's sensitivity to specific signaling molecules, while decreased expression may reduce sensitivity.

C. Activation (Agonism) of a Receptor:

- Receptor activation, or agonism, occurs when a signaling molecule (agonist) binds to its receptor and triggers a cellular response.

- Agonists can mimic the effects of endogenous ligands (natural signaling molecules) or drugs that activate receptors.
- The binding of an agonist to its receptor typically initiates a series of intracellular events, leading to physiological responses such as cell signaling, gene expression, or changes in cellular function.

D. Antagonism of a Receptor:

- Receptor antagonism occurs when a molecule (antagonist) binds to a receptor but does not activate it.
- Antagonists block or inhibit the binding of agonists to the receptor, preventing their effects.
- Antagonists can compete with agonists for binding to the receptor, effectively reducing the receptor's activation by endogenous ligands or drugs.

E. Receptor Binding:

- Receptor binding refers to the specific interaction between a signaling molecule (ligand) and its corresponding receptor.
- When a ligand binds to its receptor, it forms a complex that triggers a cellular response or physiological effect.
- The binding of a ligand to its receptor is typically selective and specific, with each receptor having a particular affinity for certain ligands.

Primary Human Kinesiological Movements and examples:

Basic Movements

1. **Flexion:** Decreasing the angle between two body parts. For example, bending the elbow or knee.
2. **Extension:** Increasing the angle between two body parts. For example, straightening the elbow or knee.

Abduction and Adduction

3. **Abduction:** Moving a body part away from the midline of the body. For example, lifting the arm or leg to the side.
4. **Adduction:** Moving a body part towards the midline of the body. For example, lowering the arm or leg back to the side of the body.

Rotation

5. **Medial (Internal) Rotation:** Rotating a limb towards the midline of the body. For example, rotating the shoulder or hip inward.

6. **Lateral (External) Rotation:** Rotating a limb away from the midline of the body. For example, rotating the shoulder or hip outward.

Circumduction

7. **Circumduction:** A circular movement that combines flexion, extension, abduction, and adduction. For example, moving the arm in a circular motion at the shoulder joint.

Special Movements (shoulder, wrist, ankle, etc.)

8. **Elevation:** Lifting a body part upwards. For example, shrugging the shoulders.
9. **Depression:** Lowering a body part downwards. For example, returning the shoulders to a resting position after a shrug.
10. **Protraction:** Moving a body part forward. For example, jutting the jaw forward or rounding the shoulders forward.
11. **Retraction:** Moving a body part backward. For example, pulling the jaw back or squeezing the shoulder blades together.
12. **Pronation:** Rotating the forearm so the palm faces downward.
13. **Supination:** Rotating the forearm so the palm faces upward.
14. **Dorsiflexion:** Bending the foot upward at the ankle.
15. **Plantarflexion:** Bending the foot downward at the ankle.
16. **Inversion:** Turning the sole of the foot inward.
17. **Eversion:** Turning the sole of the foot outward.
18. **Radial Deviation (Radial Flexion):** Moving the wrist towards the thumb side.
19. **Ulnar Deviation (Ulnar Flexion):** Moving the wrist towards the little finger side.
20. **Opposition:** Moving the thumb to touch the tips of the other fingers.
21. **Reposition:** Moving the thumb back to its normal position after opposition.

The Major Muscles of the body and their functions:

(Starting from the Neck, and ending with the Calves)

Neck Muscles

1. **Sternocleidomastoid (SCM):**
    - Function:
        - Flexion: Acting unilaterally, it rotates the head to the opposite side and tilts it laterally to the same side.
        - Extension: Acting bilaterally, it extends the head and neck.
2. **Trapezius:**

- Function:
    - Elevation: Raises and retracts the shoulders.

3. **Scalene Muscles (Anterior, Middle, and Posterior):**
    - Function:
        - Bilateral contraction assists in neck flexion and raises the first rib during forced inhalation.
        - Unilateral contraction causes ipsilateral lateral flexion of the neck and contralateral rotation.

4. **Longus Colli:**
    - Function:
        - Flexion: Flexes the neck.
        - Lateral Flexion: Tilts the neck laterally.

5. **Longus Capitis:**
    - Function:
        - Flexion: Flexes the head and neck.

6. **Levator Scapulae:**
    - Function:
        - Elevation: Elevates the scapula.
        - Downward Rotation: Rotates the scapula downward.
7. **Splenus Capitis (Capitis Superior and Capitis Inferior):**
    - Function:
        - Bilateral contraction extends the head and neck.
        - Unilateral contraction laterally flexes and rotates the head to the same side.

8. **Suboccipital Muscles (Rectus Capitis Posterior Major, Rectus Capitis Posterior Minor, Obliquus Capitis Superior, and Obliquus Capitis Inferior):**
    - Function:
        - Extension: Extend and rotate the head.

Shoulder Muscles

1. **Anterior Deltoid:**
    - Function: The anterior deltoid is primarily responsible for flexion and horizontal adduction of the shoulder joint.
    - Specific Functions:
        - Flexion: Raises the arm forward, such as when performing a front raise.
        - Horizontal Adduction: Moves the arm toward the midline of the body, as in a chest fly motion.

2. **Middle Deltoid:**
    - Function: The middle deltoid plays a key role in shoulder abduction, which involves lifting the arm away from the body in the plane of the shoulder.
    - Specific Functions:
        - Abduction: Raises the arm laterally, away from the body, such as during lateral raises.
3. **Posterior Deltoid:**
    - Function: The posterior deltoid primarily contributes to shoulder extension, horizontal abduction, and external rotation.
    - Specific Functions:
        - Extension: Moves the arm backward, such as during rowing motions.
        - Horizontal Abduction: Moves the arm away from the midline of the body, as in a reverse fly.
        - External Rotation: Rotates the arm outwardly, such as when reaching behind the back.
4. **Upper Trapezius:**
    - Origin: Occipital bone (base of the skull) and nuchal ligament.
    - Insertion: Lateral third of the clavicle.
    - Function:
        - Elevation: Raises the shoulder girdle, lifting the shoulder toward the ears.
        - Upward Rotation: Rotates the shoulder blade upward, especially in conjunction with elevation.
5. **Middle Trapezius:**
    - Origin: Spinous processes of the upper thoracic vertebrae (T1-T5).
    - Insertion: Medial border of the scapula.
    - Function:
        - Retraction: Pulls the shoulder blades together toward the spine.
        - Adduction: Moves the scapula toward the midline of the body.
6. **Lower Trapezius:**
    - Origin: Spinous processes of the lower thoracic vertebrae (T6-T12).
    - Insertion: Medial border of the scapula.
    - Function:
        - Depression: Lowers the shoulder girdle, pulling the shoulder blades downward.
        - Stabilization: Helps stabilize the scapula against the ribcage during arm movements.
7. **Levator Scapulae:**

- Function:
    - Elevates the scapula.
    - Assists in downward rotation of the scapula.

Arm Muscles

1. **Biceps Brachii Long Head:**
    - Origin: The long head originates from the supraglenoid tubercle of the scapula, which is located above the glenoid cavity.
    - Function:
        - Elbow Flexion: The long head of the biceps brachii contributes significantly to elbow flexion, which involves bending the elbow joint and bringing the forearm closer to the upper arm.
        - Shoulder Flexion: Additionally, the long head assists in shoulder flexion, particularly when the arm is in an externally rotated position. This action is important for movements such as lifting objects overhead.
2. **Biceps Brachii Short Head:**
    - Origin: The short head originates from the coracoid process of the scapula, a bony projection located on the anterior aspect of the scapula.
    - Function:
        - Elbow Flexion: Similar to the long head, the short head of the biceps brachii is involved in elbow flexion, contributing to the bending of the elbow joint.
        - Stabilization: The short head also helps stabilize the shoulder joint, particularly during movements involving heavy loads or when the shoulder is in an abducted position.
3. **Triceps Brachii Long Head:**
    - Origin: The long head originates from the infraglenoid tubercle of the scapula, which is located below the glenoid cavity.
    - Function:
        - Elbow Extension: The long head of the triceps brachii is the primary extensor of the elbow joint. It straightens the elbow, allowing for the forearm to move away from the upper arm.
        - Shoulder Extension: Additionally, the long head assists in extending the shoulder joint when the arm is raised above the head, such as during overhead movements.
4. **Triceps Brachii Lateral Head:**
    - Origin: The lateral head originates from the posterior surface of the humerus, above the radial groove.
    - Function:

- Elbow Extension: The lateral head contributes to elbow extension, working together with the long head to straighten the elbow joint.

5. **Triceps Brachii Medial Head:**
   - Origin: The medial head originates from the posterior surface of the humerus, below the radial groove.
   - Function:
     - Elbow Extension: The medial head also participates in elbow extension, assisting the other heads in straightening the elbow joint.

6. **Forearm Flexor Muscles:**
   - Function: These muscles primarily flex the wrist joint and fingers.
     - Flexor Digitorum Superficialis: Flexes the middle phalanges of the fingers.
     - Flexor Digitorum Profundus: Flexes the distal phalanges of the fingers.
     - Flexor Carpi Radialis: Flexes and abducts the wrist.
     - Flexor Carpi Ulnaris: Flexes and adducts the wrist.
     - Palmaris Longus: Weakly flexes the wrist and tenses the palmar aponeurosis.
     - Pronator Teres: Pronates the forearm and flexes the elbow.

7. **Forearm Extensor Muscles:**
   - Function: These muscles primarily extend the wrist joint and fingers.
     - Extensor Digitorum: Extends the fingers at the metacarpophalangeal and proximal interphalangeal joints.
     - Extensor Carpi Radialis Longus and Brevis: Extends and abducts the wrist.
     - Extensor Carpi Ulnaris: Extends and adducts the wrist.
     - Extensor Indicis: Extends the index finger.
     - Extensor Pollicis Longus and Brevis: Extend the thumb.
     - Supinator: Supinates the forearm.

Anterior Torso Muscles

1. **Pectoralis Major**:
   - Function:
     - Shoulder Flexion: The pectoralis major assists in flexing the shoulder joint, bringing the arm forward and across the body.
     - Shoulder Adduction: It contributes to adduction, bringing the arm towards the midline of the body.
     - Shoulder Horizontal Adduction: The pectoralis major plays a significant role in horizontal adduction, bringing the arm towards the midline of the body from a position of shoulder abduction.

        - Internal Rotation: It assists in internal rotation of the shoulder joint.
    - **Note**: The pectoralis major is a large, fan-shaped muscle covering much of the anterior chest wall.

2. **Pectoralis Minor**:
    - Function:
        - Scapular Protraction: The pectoralis minor pulls the scapula forward and towards the midline of the body.
        - Scapular Depression: It lowers the scapula.
        - Scapular Downward Rotation: The muscle rotates the scapula downwards.
    - Note: The pectoralis minor is a smaller muscle located beneath the pectoralis major.

3. **Serratus Anterior:**
    - Function:
        - Scapular Protraction: Pulls the scapula forward and around the rib cage.
        - Scapular Upward Rotation: Rotates the scapula upward.

4. **Rectus Abdominis:**
    - Function:
        - Flexion of the Trunk: Contraction of the rectus abdominis muscles brings the rib cage closer to the pelvis, resulting in forward bending of the trunk.
        - Stabilization: Helps stabilize the trunk and pelvis during movements and activities such as lifting, pushing, and pulling.
        - Assists in Forced Exhalation: Contraction of the rectus abdominis aids in expelling air from the lungs during forceful exhalation.

5. **External Oblique:**
    - Function:
        - Trunk Flexion and Rotation: Contraction of the external oblique muscles helps flex the trunk forward and rotate it to the opposite side.
        - Side Bending: The external obliques assist in lateral flexion of the trunk, bending it sideways.
        - Compression of Abdominal Contents: Contraction of the external obliques assists in compressing the abdominal contents, contributing to intra-abdominal pressure.

6. **Internal Oblique:**
    - Function:

- Trunk Flexion and Rotation: Contraction of the internal oblique muscles assists in flexing the trunk forward and rotating it to the same side.
- Side Bending: The internal obliques assist in lateral flexion of the trunk, bending it sideways.
- Compression of Abdominal Contents: Contraction of the internal obliques assists in compressing the abdominal contents, contributing to intra-abdominal pressure.

7. **Transversus Abdominis:**
    - Function:
        - Abdominal Compression: Contraction of the transversus abdominis muscles compresses the abdominal contents, providing core stability and support.
        - Assists in Forced Exhalation: Contraction of the transversus abdominis aids in expelling air from the lungs during forceful exhalation.
        - Provides Lumbar Stability: The transversus abdominis acts as a stabilizer for the lumbar spine, helping to maintain proper alignment and prevent injury.

Posterior Torso Muscles

1. **Trapezius:**
    - Function:
        - Upper Fibers: Elevate and upwardly rotate the scapula (shoulder blade).
        - Middle Fibers: Retract the scapula.
        - Lower Fibers: Depress and upwardly rotate the scapula.
2. **Teres Major**:
    - Function:
        - Shoulder Adduction: The teres major assists in adducting the shoulder joint, bringing the upper arm towards the midline of the body.
        - Medial Rotation: It also contributes to the medial rotation of the shoulder joint, turning the arm inward.
        - Extension: The teres major aids in extending the shoulder joint, moving the arm backward.
3. **Teres Minor**:
    - Function:
        - Shoulder External Rotation: The teres minor is one of the primary external rotators of the shoulder joint, rotating the arm outward.

- Stabilization: It helps stabilize the shoulder joint, particularly during movements involving overhead reaching or throwing.
- Assists in Adduction: The teres minor also assists in adducting the arm, bringing it towards the midline of the body.

4. **Latissimus Dorsi:**
    - Function:
        - Shoulder Extension: Pulls the upper arm downward and backward, as in pulling movements (e.g., pull-ups, rows).
        - Shoulder Adduction: Brings the upper arm toward the body.
        - Shoulder Internal Rotation: Medially rotates the upper arm.
5. **Erector Spinae Group (Iliocostalis, Longissimus, Spinalis):**
    - Function:
        - Spinal Extension: Straightens and extends the spine.
        - Lateral Flexion: Bends the spine sideways.
        - Spinal Rotation: Rotates the spine.
6. **Rhomboids (Major and Minor):**
    - Function:
        - Retraction: Pulls the scapula towards the spine.
        - Downward Rotation: Rotates the scapula downward.

Leg Muscles

1. **Gluteus Maximus (Glutes):**
    - Upper Fibers:
        - Function: Hip Extension
            - The upper fibers of the gluteus maximus primarily function to extend the hip joint, moving the thigh backward from a flexed position.
    - Lower Fibers:
        - Function: Hip External Rotation
            - The lower fibers of the gluteus maximus contribute to external rotation of the hip joint, turning the thigh outward.
2. **Gluteus Medius:**
    - Anterior Fibers:
        - Function: Hip Flexion, Abduction, and Internal Rotation
            - The anterior fibers of the gluteus medius assist in flexing the hip joint, moving the thigh forward. They also play a significant role in abduction, lifting the leg away from the midline of the body, and internal rotation of the hip joint.
    - Posterior Fibers:
        - Function: Hip Extension, Abduction, and External Rotation

- The posterior fibers of the gluteus medius contribute to hip extension, abduction, and external rotation of the hip joint.

3. **Gluteus Minimus:**
    - Function: Hip Flexion, Abduction, and Internal Rotation
        - The gluteus minimus assists in flexing the hip joint, abducting the thigh, and internally rotating the hip joint.

4. **Quadricep Rectus Femoris:**
    - Function:
        - Knee Extension: The rectus femoris is the only quadriceps muscle that crosses both the hip and knee joints. It primarily functions to extend the knee joint, straightening the leg from a bent position.
        - Hip Flexion: In addition to its role in knee extension, the rectus femoris assists in flexing the hip joint, bringing the thigh towards the abdomen.

5. **Quadricep Vastus Lateralis:**
    - Function:
        - Knee Extension: The vastus lateralis primarily works to extend the knee joint, assisting in straightening the leg.

6. **Quadricep Vastus Medialis:**
    - Function:
        - Knee Extension: The vastus medialis also primarily functions to extend the knee joint, contributing to the straightening of the leg.

7. **Quadricep Vastus Intermedius:**
    - Function:
        - Knee Extension: The vastus intermedius, like the other quadriceps muscles, plays a key role in extending the knee joint, helping to straighten the leg.

8. **Hamstring Biceps Femoris:**
    - Function:
        - Knee Flexion: The biceps femoris, both the long head and short head, primarily function to flex the knee joint, bending the leg.
        - Hip Extension: Additionally, the biceps femoris assists in extending the hip joint, moving the thigh backward.
        - Lateral Rotation: The long head of the biceps femoris also contributes to the lateral rotation of the thigh at the hip joint.

9. **Hamstring Semitendinosus:**
    - Function:
        - Knee Flexion: The semitendinosus primarily functions to flex the knee joint, aiding in bending the leg.

- Hip Extension: Additionally, the semitendinosus assists in extending the hip joint, moving the thigh backward.
- Medial Rotation: The semitendinosus also contributes to the medial rotation of the thigh at the hip joint.

10. **Hamstring Semimembranosus:**
    - Function:
        - Knee Flexion: The semimembranosus also primarily functions to flex the knee joint, assisting in bending the leg.
        - Hip Extension: Additionally, the semimembranosus assists in extending the hip joint, moving the thigh backward.
        - Medial Rotation: The semimembranosus contributes to the medial rotation of the thigh at the hip joint.

11. **Adductor Magnus (Groin)**:
    - Function: Adduction of the Thigh
        - The adductor magnus muscle is the largest and strongest muscle of the adductor group. It primarily functions to adduct the thigh, bringing it towards the midline of the body.
    - Other Functions: The adductor magnus also assists in hip extension and stabilization of the pelvis.

12. **Adductor Longus and Adductor Brevis (Groin)**:
    - Function: Adduction of the Thigh
        - Both the adductor longus and adductor brevis muscles contribute to adduction of the thigh, pulling it towards the midline of the body.

13. **Gastrocnemius (Calve):**
    - Function:
        - Plantar Flexion: The gastrocnemius is the larger calf muscle and plays a significant role in plantar flexion, pointing the foot downward.
        - Knee Flexion: Additionally, the gastrocnemius assists in flexing the knee joint when the foot is dorsiflexed (bent upward), as in movements such as squatting and lunging.
        - Stabilization: The gastrocnemius helps stabilize the ankle joint during weight-bearing activities like walking, running, and jumping.

14. **Soleus:**
    - Function:
        - Plantar Flexion: The soleus is a deeper calf muscle that primarily contributes to plantar flexion of the foot, particularly when the knee is bent.

- Stabilization: The soleus also helps stabilize the ankle joint and control movements of the foot during weight-bearing activities.

15. **Plantaris:**
    - Function:
        - Plantar Flexion: The plantaris is a smaller calf muscle that assists in plantar flexion of the foot.
        - Knee Flexion: It also plays a minor role in flexing the knee joint, particularly when the foot is dorsiflexed.

16. **Tibialis Posterior:**
    - Function:
        - Plantar Flexion: The tibialis posterior is located deep in the calf and contributes to plantar flexion of the foot.
        - Inversion: Additionally, the tibialis posterior assists in inversion of the foot, turning the sole inward.

Fatty Acids and their Carbon Notations (Carbon Atom Identifiers)

Saturated Fatty Acids (SFAs)

1. **Butyric Acid (C4:0)**
    - Sources: Butter, milk, cheese.
    - Classification: Short-chain.
2. **Caproic Acid (C6:0)**
    - Sources: Goat milk, certain cheeses.
    - Classification: Short-chain.
3. **Caprylic Acid (C8:0)**
    - Sources: Coconut oil, palm kernel oil, goat milk.
    - Classification: Medium-chain.
4. **Capric Acid (C10:0)**
    - Sources: Coconut oil, palm kernel oil, goat milk.
    - Classification: Medium-chain.
5. **Lauric Acid (C12:0)**
    - Sources: Coconut oil, palm kernel oil.
    - Classification: Medium-chain.
6. **Myristic Acid (C14:0)**
    - Sources: Coconut oil, palm kernel oil, dairy products.
    - Classification: Medium-chain.
7. **Palmitic Acid (C16:0)**
    - Sources: Palm oil, meat, dairy products.
    - Classification: Long-chain.
8. **Stearic Acid (C18:0)**
    - Sources: Beef, cocoa butter, lard.

- Classification: Long-chain.

Monounsaturated Fatty Acids (MUFAs)

1. **Palmitoleic Acid (C16:1)**
    - Sources: Fish oil, macadamia nuts, some animal fats.
    - Classification: Long-chain.
2. **Oleic Acid (C18:1n-9)**
    - Sources: Olive oil, avocados, nuts, seeds.
    - Classification: Long-chain.

Polyunsaturated Fatty Acids (PUFAs)

1. **Linoleic Acid (C18:2n-6)**
    - Sources: Vegetable oils (corn oil, soybean oil, sunflower oil), nuts, seeds.
    - Classification: Omega-6, long-chain.
2. **Alpha-Linolenic Acid (ALA) (C18:3n-3)**
    - Sources: Flaxseed oil, chia seeds, walnuts.
    - Classification: Omega-3, long-chain.
3. **Gamma-Linolenic Acid (GLA) (C18:3n-6)**
    - Sources: Evening primrose oil, borage oil, black currant seed oil.
    - Classification: Omega-6, long-chain.
4. **Arachidonic Acid (C20:4n-6)**
    - Sources: Meat, eggs, dairy products.
    - Classification: Omega-6, long-chain.
5. **Eicosapentaenoic Acid (EPA) (C20:5n-3)**
    - Sources: Fish oil, algae oil.
    - Classification: Omega-3, long-chain.
6. **Docosahexaenoic Acid (DHA) (C22:6n-3)**
    - Sources: Fish oil, algae oil.
    - Classification: Omega-3, long-chain.
7. **Conjugated Linoleic Acid (CLA) (C18:2 c9, t11) (C18:2 t10, c12)**
    - Sources: Meat and dairy products from ruminants (cows, sheep, goats).
    - Classification: Conjugated fatty acid.

Trans Fatty Acids

1. **Elaidic Acid (C18:1 t9)**
    - Sources: Partially hydrogenated vegetable oils, processed foods
    - Classification: Trans-fat.

Glossary

This is not a full list of terminology used in this book, it is an introductory list of biomedical research terminology definitions I have extracted predominately from *ChatGPT* and *arduously* organized alphabetically relating directing to the material within and in relation to the sciences covered in this work.

#

3xTg-AD mice: Transgenic mouse model expressing mutant human genes associated with Alzheimer's disease (APP, PS1, and tau), used to study disease progression and test potential therapies.
4E-BP1/2: Eukaryotic initiation factor 4E (eIF4E)-binding proteins that regulate mRNA translation by binding to eIF4E, modulating protein synthesis.
5-bromo-2'-deoxyuridine (BrdU)-labeled c: Assay used to study cell proliferation and DNA synthesis, involving the incorporation of BrdU into newly synthesized DNA during cell division, followed by immunostaining or detection of BrdU incorporation.

A

Aβ25-35: Short fragment of amyloid beta peptide implicated in Alzheimer's disease pathology, known for its neurotoxic effects.
Ablation: Removal or destruction of tissue or cells, often performed surgically or using chemical or thermal methods.
Acetate: Short-chain fatty acid produced by microbial fermentation in the gut, serving as an energy source for various tissues and influencing metabolism.
Adhesion: Process by which cells attach to one another or to the extracellular matrix, crucial for tissue structure, immune responses, and cellular communication.
Aerobic: Metabolic process occurring in the presence of oxygen, producing ATP through oxidative phosphorylation in mitochondria.
Aerobic Respiration: Cellular process using oxygen to break down glucose into ATP, water, and carbon dioxide for energy production.
Acetylcholine (Ach): Neurotransmitter responsible for transmitting signals across synapses in the nervous system, involved in muscle contraction, learning, and memory.
Acetylcholinesterase (AChE): Enzyme that hydrolyzes acetylcholine into choline and acetate, terminating its action at the synaptic cleft.
Actin: Globular protein forming microfilaments involved in cellular structure, motility, and muscle contraction.
Action Potential: Rapid, transient change in membrane potential of excitable cells, propagating along the length of nerve fibers or muscle cells.
Actomyosin: Complex formed by the interaction of actin and myosin filaments during muscle contraction, generating force and movement.

Adaptive Immune System: Branch of the immune system characterized by specificity, memory, and the ability to adapt to new pathogens or antigens.
Adenosine Triphosphate (ATP): Nucleotide molecule serving as the primary energy currency of cells, storing and transferring energy for cellular processes.
Adenosine Monophosphate (AMP): Nucleotide molecule composed of adenine, ribose, and a single phosphate group, serving as a precursor for ATP synthesis.
Adenosine Diphosphate (ADP): Nucleotide molecule composed of adenine, ribose, and two phosphate groups, formed by hydrolysis of ATP.
Adenosine: Nucleoside molecule derived from adenine and ribose, involved in neurotransmission, vasodilation, and modulating immune response.
Adenylate Cyclase: Enzyme catalyzing the conversion of ATP to cyclic AMP (cAMP), a second messenger involved in cellular signaling pathways.
Adipocyte: Cell specialized in storing fat, crucial for energy regulation and body composition, found in adipose tissue.
Adipokines: Signaling molecules secreted by adipose tissue, regulating metabolism, inflammation, and energy balance, including leptin and adiponectin.
Adipose Tissue: Connective tissue composed of adipocytes (fat cells) storing energy in the form of triglycerides and regulating metabolism.
Afferent Neuron: Sensory neuron transmitting information from peripheral receptors to the central nervous system (brain or spinal cord).
Affinity: Measure of the strength of binding between a ligand and its receptor, determined by the dissociation constant (Kd).
Agonist (Receptor): Molecule that binds to a receptor and activates its signaling pathway, mimicking the effects of endogenous ligands.
AICAR (5-Aminoimidazole-4-carboxamide ribonucleotide): Activator of AMP-activated protein kinase (AMPK), used in research to mimic the effects of exercise on metabolism.
Amino Acid: Organic molecule containing an amino group, carboxyl group, and variable side chain, serving as the building blocks of proteins.
Ammonia: A colorless gas with a pungent odor, composed of nitrogen and hydrogen, produced through the breakdown of nitrogen-containing compounds, such as amino acids, during metabolism.
AMP-activated protein kinase (AMPK): Cellular energy sensor activated by low ATP levels, regulating metabolism, autophagy, and mitochondrial biogenesis.
AMPA Receptors: Ionotropic glutamate receptors mediating fast excitatory neurotransmission in the central nervous system.
Amyloid precursor protein (APP): A transmembrane protein involved in synaptic function, whose abnormal processing can lead to amyloid plaque formation, associated with Alzheimer's disease.
Anaerobic: Metabolic process occurring in the absence of oxygen, generating energy through glycolysis and fermentation.
Androgens: Steroid hormones, such as testosterone, responsible for male sexual development and reproductive function, also influencing muscle growth and metabolism.
Angiogenesis: The process of new blood vessel formation from pre-existing vessels, crucial for tissue growth, wound healing, and tumor development.

Antagonist (Receptor): Molecule that binds to a receptor and blocks its activation by endogenous ligands, inhibiting downstream signaling pathways.
Antibody: Protein molecule produced by B cells in response to specific antigens, capable of binding to and neutralizing pathogens or foreign molecules.
Antigen: Molecule recognized by the immune system as foreign, triggering an immune response, including antibodies and T cell activation.
Antinociception: The physiological process of reducing or blocking the perception of pain signals in the nervous system.
Apoptosis: Programmed cell death characterized by controlled dismantling of cellular components, crucial for tissue homeostasis and development.
APP/PS1 mice: Transgenic mice model expressing human amyloid precursor protein (APP) and presenilin 1 (PS1) genes, commonly used in Alzheimer's disease research.
APPsw mice: Transgenic mice model expressing mutant amyloid precursor protein (APP), often used to study amyloid plaque deposition in Alzheimer's disease.
Astrocyte: Star-shaped glial cells in the brain and spinal cord, providing structural support and metabolic regulation to neurons.
Atrogenes: Genes involved in muscle atrophy, including MAFbx and Atrogin-1, encoding E3 ubiquitin ligases that target muscle proteins for degradation.
Atrogin-1: Muscle-specific E3 ubiquitin ligase involved in ubiquitin-mediated proteolysis and muscle atrophy.
Area Under the Curve (AUC): Measure of the total exposure to a drug or substance over time, calculated by integrating the concentration-time curve.
Autocrine: Signaling mechanism in which a cell secretes signaling molecules (autocrine factors) that act on the same cell or cells of the same type.
Autophagy: Cellular process of degrading and recycling damaged organelles and proteins, promoting cell survival during stress and starvation.
ANCOVA (Analysis of Covariance): Statistical method used to compare group means while accounting for the influence of one or more covariates.
Autofluorescence: Natural fluorescence emitted by certain molecules (e.g., flavins, lipofuscin) upon excitation by light, often used for imaging and diagnostic purposes.
Axons: Long, slender projection of a nerve cell (neuron) that conducts electrical impulses away from the cell body to other neurons or effector cells.

B

BALB/cJ mice: Inbred strain of laboratory mice commonly used in biomedical research due to their docile nature and susceptibility to various diseases.
Basic Fibroblast Growth Factor (bFGF): Growth factor involved in cell proliferation, differentiation, and angiogenesis, promoting tissue repair and regeneration.
Bax: Pro-apoptotic protein belonging to the Bcl-2 family, involved in the intrinsic pathway of apoptosis by promoting mitochondrial outer membrane permeabilization.
Bcl-2: Anti-apoptotic protein belonging to the Bcl-2 family, inhibiting apoptosis by regulating mitochondrial membrane integrity and caspase activation.
B-Catenin: Protein involved in Wnt signaling pathway, regulating gene expression and cell proliferation during development and tissue homeostasis.

B Cells: Type of white blood cell involved in adaptive immunity, producing antibodies and mediating humoral immune responses.
Bioavailability: The proportion of a drug or substance that enters the bloodstream and becomes available for systemic circulation or distribution to target tissues after administration.
Biochemical Cascade: Series of interconnected biochemical reactions or signaling events, often amplifying and transmitting cellular signals or responses.
Brown fat: A type of adipose tissue that generates heat by burning calories, helping to regulate body temperature and metabolism.
BTBR mice: Inbred strain of laboratory mice commonly used as a model for autism spectrum disorders due to their social deficits and repetitive behaviors.
Butyrate: Short-chain fatty acid produced by microbial fermentation of dietary fiber in the colon, serving as an energy source for colonocytes and regulating gene expression.

C

C2C12 myoblast: Murine skeletal muscle cell line commonly used in cell culture studies of myogenesis and muscle differentiation.
C57BL/J mice: Inbred strain of laboratory mice commonly used in biomedical research for their genetic homogeneity and susceptibility to specific diseases.
CA1-CA3: Subfields of the hippocampus involved in memory formation and spatial navigation, susceptible to damage in neurodegenerative diseases.
Caenorhabditis elegans: Transparent, free-living nematode used as a model organism in genetic and developmental studies.
Calcineurin: Calcium-dependent protein phosphatase involved in signal transduction pathways regulating gene expression, metabolism, and muscle function.
Calcium/Calmodulin-Dependent Protein Kinase Kinase Beta (CaMKKB): Protein kinase activated by calcium/calmodulin complex, regulating cellular responses to calcium signals.
Calmodulin: Calcium-binding protein involved in intracellular signaling pathways, regulating the activity of various enzymes and proteins.
Calpains: Enzymes responsible for protein cleavage involved in various cellular processes like cell migration, apoptosis, and signal transduction.
CAM assay (Chorioallantoic Membrane assay): Method used to assess angiogenesis and tumor growth by implanting tissue or cells onto the chorioallantoic membrane of chick embryos.
cAMP Response Element-Binding protein (CREB): Transcription factor activated by cAMP signaling, regulating gene expression in response to various stimuli.
Carbohydrate: Organic compound composed of carbon, hydrogen, and oxygen atoms, serving as a major source of energy and structural component in living organisms.
Caspases: Proteolytic enzymes involved in apoptosis and inflammation, cleaving cellular substrates and promoting cell death.
Catalase (CAT): Enzyme that catalyzes the decomposition of hydrogen peroxide into water and oxygen, protecting cells from oxidative stress.
Catecholamine: Class of neurotransmitters and hormones, including dopamine, norepinephrine, and epinephrine, involved in regulating mood, arousal, and stress responses.
Catalyze: To accelerate or facilitate a chemical reaction without undergoing any permanent change or being consumed in the process.

CD8T Cells: Cytotoxic T lymphocytes expressing CD8 co-receptor, involved in cell-mediated immunity by recognizing and killing infected or abnormal cells.
Cellular Remodeling: Process of structural and functional changes in cells, tissues, or organs, often in response to physiological stimuli or pathological conditions.
Cell Viability: Measure of the ability of cells to survive and proliferate under specific conditions, often assessed using various assays.
Ceramide: Lipid molecule involved in cell signaling pathways regulating apoptosis, cell differentiation, and stress response.
Cerebrospinal fluid: Clear, colorless fluid circulating around the brain and spinal cord, providing cushioning and nutritional support.
Cell Membrane: Phospholipid bilayer surrounding the cytoplasm of cells, regulating the passage of molecules and ions into and out of the cell.
Chelation: Chemical process of forming a complex between a metal ion and a chelating agent, used to remove toxic metals from the body or inhibit metal-dependent enzymes.
Chromatin: Complex of DNA, histone proteins, and other proteins, forming the structural basis of chromosomes and regulating gene expression.
Cmax: Maximum concentration of a drug or substance achieved in the body after administration, often used as a pharmacokinetic parameter.
Chronic unpredictable stress: A laboratory model inducing stress in mice via varied and unpredictable stressors over time, used to study stress-related behaviors and physiological responses.
Coenzyme: Non-protein organic molecule required for the activity of certain enzymes, often serving as a carrier for chemical groups or electrons.
Collagen: Fibrous protein providing structural support and strength to tissues such as skin, tendons, and bones, forming the extracellular matrix.
Colocalization: Spatial overlap or coincidence of two or more molecules or structures within cells, indicating potential interaction or functional relationship.
Conditioned place preference: Behavioral paradigm used to measure the rewarding effects of drugs or environmental stimuli by associating them with specific contexts or environments.
Conduction: The transmission or propagation of electrical impulses or signals within biological tissues or along neural pathways.
Corona: A layer of proteins that forms on the surface of nanoparticles when they come into contact with biological fluids, capable of influencing biological barrier entry.
Costamere: Protein complex linking the sarcomere to the sarcolemma and extracellular matrix, providing structural support and transmitting force during muscle contraction.
Control (Study design): A group in an experiment used as a baseline for comparison with the experimental group receiving the intervention.
CUPRAC (Cupric Ion Reducing Antioxidant Capacity): Assay used to measure the total antioxidant capacity of biological samples based on their ability to reduce cupric ions to cuprous ions.
Cross maze: Behavioral test used to assess spatial learning and memory in rodents by requiring them to navigate through intersecting arms to find a hidden goal.
Cross-sectional Area (muscle): Measure of the area of a muscle perpendicular to its longitudinal axis, often used to assess muscle size or hypertrophy.

Cued memory: Recollection of information triggered by a specific cue or stimulus associated with the original learning experience.
Cyclic adenosine monophosphate (cAMP): A signaling molecule involved in numerous cellular processes, including metabolism, gene expression, and neurotransmission.
Cytochrome: A heme-containing protein involved in electron transport in cellular respiration and other metabolic processes.
Cytokine: Signaling molecule secreted by immune cells, regulating inflammation, immune responses, and cell-to-cell communication.
Cytotoxicity: Ability of a substance or agent to cause cell death or damage, often assessed in vitro using cell viability assays.

D

2,2-diphenyl-1-picrylhydrazyl (DPPH): A stable free radical compound used to assess antioxidant activity in substances. It changes color upon reduction by antioxidants.
DAF-16: Transcription factor involved in the regulation of lifespan and stress response in Caenorhabditis elegans, homologous to mammalian FOXO proteins.
DAF-2: Insulin/insulin-like growth factor receptor in Caenorhabditis elegans, regulating lifespan, stress resistance, and development.
DAT (Dopamine Transporters): Membrane proteins that regulate the reuptake of dopamine from the synaptic cleft into presynaptic neurons, terminating its action.
Deacetylation: Removal of acetyl groups from histone proteins by histone deacetylases (HDACs), associated with gene repression and transcriptional silencing.
Dendrite: Branched extension of a neuron's cell body, receiving signals from other neurons and conveying them toward the cell body.
Dentate Gyrus: Region of the hippocampus involved in learning and memory processes, particularly spatial memory and pattern separation.
Desmin: Intermediate filament protein found in muscle cells, maintaining structural integrity and providing mechanical support to muscle fibers.
ddY mice: Outbred strain of laboratory mice commonly used in toxicology and carcinogenicity studies due to their genetic diversity.
Differentiation: Process by which cells become specialized in structure and function during development or tissue regeneration.
DNA: Molecule carrying genetic information in all living organisms, consisting of a double helix structure composed of nucleotide base pairs.
DNA Fragmentation: Breakage of DNA molecules into smaller fragments, occurring during apoptosis or DNA damage.
DNA Repair: Cellular process that restores damaged DNA to its original state, maintaining genomic stability and preventing mutations.
DOMS (Delayed Onset Muscle Soreness): The vital and delayed inflammatory intramuscular rise in COX-2 expression experienced following highly damaging or acutely experienced exercise leading to enhanced nociception (soreness), and muscle hypertrophy.
DOPAC (3,4-Dihydroxyphenylacetic acid): Metabolite of dopamine formed by the action of monoamine oxidase (MAO), used as a marker of dopamine turnover.

Dopamine: Neurotransmitter involved in reward, motivation, motor control, and various cognitive functions, implicated in addiction and neurological disorders.
Downregulation: Process of reducing the expression or activity of a gene, protein, or cellular component, often in response to specific signals or conditions.
Downstream Pathway: Sequence of biochemical reactions or signaling events initiated by activation of a cell surface receptor or intracellular molecule.
DMSO (Dimethyl sulfoxide): Solvent commonly used to dissolve hydrophobic compounds and drugs for cell culture or in vivo experiments.
Drosophila melanogaster: Common fruit fly used as a model organism in genetics, developmental biology, and neuroscience research.
Duchenne muscular dystrophy: Inherited neuromuscular disorder characterized by progressive muscle weakness and wasting due to mutations in the dystrophin gene.
Dysbiosis: Imbalance or disruption of the normal microbial community (microbiota) in a particular environment, associated with various diseases or conditions.

E

Edema: Accumulation of fluid in the interstitial spaces, causing swelling and tissue inflammation.
EdU Assay (5-ethynyl-2'-deoxyuridine Assay): Method used to label proliferating cells by incorporating EdU into newly synthesized DNA during DNA replication.
Eight-arm radial maze: Behavioral test used to assess spatial learning and memory in rodents by requiring them to visit all arms of a maze to find food rewards.
Electroencephalography (EEG): A non-invasive technique used to record and analyze electrical activity in the brain.
Electromyography: Diagnostic technique used to assess the electrical activity of muscles, often used to diagnose neuromuscular disorders.
Elevated plus maze: Behavioral test used to assess anxiety-like behavior in rodents by measuring the time spent in open and closed arms of a plus-shaped maze elevated above the ground.
ELISA (Enzyme-Linked Immunosorbent Assay): Laboratory technique used to detect and quantify proteins or other molecules based on antigen-antibody interactions.
Encode: Process of converting genetic information into functional proteins or RNA molecules, regulated by gene expression and transcriptional machinery.
Endocytose: Process by which cells internalize extracellular molecules or particles by invaginating the cell membrane to form vesicles.
Endothelial Progenitor Cell: Multipotent cell derived from bone marrow or vascular tissues, capable of differentiating into endothelial cells and promoting vascular repair and angiogenesis.
Enhanced: *A person that uses Anabolic Steroids, or Growth Hormone, giving them a myogenic and lipolytic advantage*.
eNOS (Endothelial Nitric Oxide Synthase): Enzyme responsible for producing nitric oxide (NO) in endothelial cells, regulating blood vessel dilation and blood pressure.
Entropy: A measure of disorder or randomness in a system, often associated with the dispersal of energy or the tendency towards equilibrium.

Enzyme: Protein catalyst facilitating chemical reactions in living organisms by speeding up the rate of specific biochemical reactions.
Epigenetic: Heritable changes in gene expression or cellular phenotype that do not involve alterations in DNA sequence, often mediated by modifications to histones or DNA methylation.
Epinephrine (Adrenaline): Hormone and neurotransmitter that mediates the body's "fight or flight" response, increasing heart rate, blood pressure, and energy availability.
ERK1/2 (Extracellular Signal-Regulated Kinase 1/2): Subtype of MAPK activated by growth factors and mitogens, regulating cell proliferation and survival.
Estrogens: Steroid hormones, such as estradiol, responsible for female sexual development and reproductive function, also influencing bone density and cardiovascular health.
Erythrocyte: Red blood cell responsible for transporting oxygen from the lungs to tissues and carbon dioxide from tissues to the lungs.
Eukaryote: Organism with cells containing a nucleus and membrane-bound organelles, distinct from prokaryotes.
Excitatory Postsynaptic Potential (EPSP): Depolarization of the postsynaptic membrane in response to neurotransmitter binding at excitatory synapses, increasing the likelihood of an action potential.
Excitotoxicity: Pathological process resulting from excessive activation of excitatory neurotransmitter receptors, leading to neuronal damage or death.
Expression (Genetic): Process by which genetic information encoded in DNA is converted into functional gene products, such as proteins or RNA molecules.
Extracellular: Outside the cell, referring to the external environment surrounding cells or tissues.
Extracellular Matrix: Supportive network surrounding cells, influencing cellular behavior and regulating tissue function and structure.

F

FAK (Focal Adhesion Kinase): Protein kinase involved in integrin-mediated signaling, regulating cell adhesion, migration, and survival.
Fermentation: Metabolic process that generates ATP by converting carbohydrates into organic acids or alcohol in the absence of oxygen.
Fibrillogenesis: Process of forming fibrillar structures from protein monomers or peptides, occurring in various biological processes such as collagen formation.
Fibroblast: Connective tissue cell responsible for producing extracellular matrix components such as collagen and fibronectin, involved in wound healing and tissue repair.
Fibrosis: Pathological process characterized by excessive deposition of extracellular matrix components such as collagen, leading to tissue scarring and dysfunction.
Flt-1: Vascular endothelial growth factor receptor 1 (VEGFR-1), involved in angiogenesis, vascular permeability, and endothelial cell survival.
Fold (describing mathematical change): Measure of change in quantity or concentration, expressed as a multiple or ratio relative to a reference value.
Follistatin: Protein that binds and inhibits activin, a member of the TGF-beta superfamily, regulating cell proliferation, differentiation, and metabolism.
FOXO4: Transcription factor belonging to the FOXO family, involved in regulating cellular processes such as apoptosis, metabolism, and oxidative stress response.

FRAP (Fluorescence Recovery After Photobleaching): Technique used to study the dynamics of fluorescently labeled molecules within living cells by bleaching a defined region and monitoring fluorescence recovery over time.
Free radical scavenger: A substance that neutralizes harmful free radicals by donating electrons, thereby reducing oxidative stress and cellular damage.
fMRI: Functional Magnetic Resonance Imaging, a neuroimaging technique measuring brain activity by detecting changes in blood flow.
Frontal lobe: Brain region responsible for higher-level functions such as decision-making, planning, and voluntary movement control.

G

GABA (Gamma-Aminobutyric Acid): Inhibitory neurotransmitter in the central nervous system, regulating neuronal excitability and anxiety.
Genetic code: Instructions within DNA or RNA determining the sequence of amino acids in proteins during cellular protein synthesis.
GFAP (Glial Fibrillary Acidic Protein): A protein primarily found in astrocytes, used as a marker for these cells in neural tissue.
Glucocorticoid: Steroid hormone produced by the adrenal glands, regulating metabolism, immune response, and stress adaptation.
Glutathione peroxidase (GPx): An enzyme that catalyzes the reduction of hydrogen peroxide and organic hydroperoxides, protecting cells from oxidative damage.
Glycolysis: Metabolic pathway converting glucose into pyruvate, generating ATP and NADH in the cytoplasm.
Glial Cell: Non-neuronal cells of the nervous system, including astrocytes, oligodendrocytes, and microglia, providing support and regulating neuronal function.
Glial Cell line-derived neurotrophic Factor (GDNF): Neurotrophic factor promoting the survival and differentiation of neurons, particularly dopaminergic neurons, implicated in neuroprotection and neuroregeneration.
Glial fibrillary acidic protein (GFAP): Intermediate filament protein found in glial cells, such as astrocytes and Schwann cells, providing structural support and regulating cellular processes.
Gluconeogenesis: Metabolic process synthesizing glucose from non-carbohydrate precursors such as amino acids or glycerol, maintaining blood glucose levels during fasting.
Glutamate: Major excitatory neurotransmitter in the central nervous system, involved in synaptic transmission, learning, and memory.
Glutathione: Tripeptide (gamma-glutamyl-cysteinyl-glycine) antioxidant involved in cellular defense against oxidative stress and detoxification of reactive oxygen species.
Glutathione S-transferase: Enzyme that catalyzes the conjugation of glutathione to electrophilic compounds, facilitating their detoxification and elimination.
Glycine: Inhibitory neurotransmitter in the central nervous system, regulating neuronal excitability and motor control.
Glycolysis: The metabolic pathway that breaks down glucose into pyruvate, producing ATP and NADH as energy sources.
Golgi Tendon: Sensory receptor located in tendons, responding to changes in muscle tension and providing feedback to the central nervous system.

GSK3B (Glycogen Synthase Kinase 3 Beta): Serine/threonine protein kinase involved in cell signaling pathways regulating glycogen metabolism, apoptosis, and cell fate.

H

H2O2 (Hydrogen Peroxide): Reactive oxygen species (ROS) produced as a byproduct of cellular metabolism, involved in signaling and oxidative stress.
Half-Life: Time required for the concentration of a substance in the body to decrease by half through elimination or metabolism.
Heme oxygenase 1: Enzyme involved in heme catabolism, converting heme into biliverdin, carbon monoxide, and iron, with antioxidant and cytoprotective effects.
Hemodynamic: Relating to the forces and factors involved in the circulation of blood within the body, including blood pressure, flow, and resistance.
Heritability: Proportion of phenotypic variation in a population attributed to genetic factors, often estimated using twin or family studies.
HIF-1a (Hypoxia-Inducible Factor 1 Alpha): Transcription factor regulating cellular responses to hypoxia, promoting adaptation to low oxygen conditions.
Histamine: Biogenic amine involved in allergic reactions, inflammation, and neurotransmission, released by mast cells and basophils.
Histone Acetylation: Post-translational modification of histone proteins by acetyl groups, associated with gene activation and transcriptional activity.
Histone Code Hypothesis: Theory proposing that specific patterns of histone modifications act as a "code" regulating chromatin structure and gene expression.
Homeostasis: The body's ability to maintain stable internal conditions despite external changes, ensuring optimal functioning of cells and organs.
Homing (Cellular): Directed migration of cells to specific tissues or organs guided by chemical signals or receptors.
Homovanillic acid: Metabolite of dopamine, formed by the action of monoamine oxidase (MAO), used as a biomarker for dopamine turnover in the brain.
Hormone: Signaling molecule secreted by glands or cells into the bloodstream, regulating various physiological processes in distant target tissues.
Hormesis: Biphasic dose-response phenomenon characterized by low-dose stimulation and high-dose inhibition of biological processes or toxicological effects.
Hormetic: Biological response characterized by biphasic dose-response curves, where low doses of a stressor have beneficial effects, while high doses are harmful.
HPLC analysis: High-performance liquid chromatography (HPLC) technique used to separate, identify, and quantify components in complex mixtures, based on their interaction with a stationary phase and mobile phase.
Humoral Immunity: Branch of the immune system involving the production of antibodies by B cells, providing defense against pathogens circulating in bodily fluids.
HUVEC (Human Umbilical Vein Endothelial Cells): Primary cell culture model derived from human umbilical veins, commonly used in vascular biology and angiogenesis research.
Hyperplasia: Increase in the number of cells in a tissue or organ, resulting from cell proliferation.

Hypothalamic Pituitary Axis (HPA): A regulatory system involving the hypothalamus, pituitary gland, and adrenal glands, controlling stress response and hormone secretion.
Hypoxia: Condition characterized by decreased oxygen levels in tissues or organs, often associated with ischemia or inadequate blood supply.

I

ICAM-1 (Intercellular Adhesion Molecule-1): A cell surface protein involved in the adhesion of leukocytes to endothelial cells during inflammation and immune responses.
Immunocytochemistry: Laboratory technique used to visualize and localize specific proteins or antigens within cells using antibodies and fluorescent or enzymatic detection methods.
Immunoglobulins: Family of proteins comprising antibodies, involved in immune responses by recognizing and binding to specific antigens.
Immortalized (cell line): A population of cells that have been altered to bypass normal cellular aging processes, allowing them to proliferate indefinitely in culture while maintaining their original genetic characteristics.
Inhibitor of kappa B alpha (IκBα): A protein that regulates the activity of the transcription factor NF-κB by sequestering it in the cytoplasm.
iNOS (Inducible Nitric Oxide Synthase): Enzyme responsible for producing nitric oxide (NO) in response to inflammatory stimuli, involved in host defense and immune responses.
In silico docking: Computational technique used to predict the binding interactions between small molecules (ligands) and protein targets (receptors), aiding drug discovery and design.
Insult: Biological or environmental stressor causing injury or damage to cells or tissues, triggering adaptive responses or pathological processes.
Intercellular: Between cells, referring to communication or interactions occurring among neighboring cells.
Interferons: Group of cytokines involved in antiviral defense, immune regulation, and modulation of inflammatory responses.
Interleukin: Group of cytokines produced by leukocytes and other cells, regulating immune responses, inflammation, and hematopoiesis.
Interstitial fluid: Fluid surrounding cells in tissues, transporting nutrients, gases, and waste products between cells and blood vessels.
Intraperitoneal (administration): Method of drug or substance administration involving injection into the peritoneal cavity, often used in animal studies for systemic delivery.
In vitro: Latin term meaning "in glass," referring to experiments or observations conducted outside of living organisms, often in cell culture or artificial environments.
In vivo: Latin term meaning "within the living," referring to experiments or observations conducted in living organisms.
Ion: Atom or molecule with a net electrical charge due to the loss or gain of electrons.
Ion Channel: Transmembrane protein that forms a pore in the cell membrane, allowing selective passage of ions across the membrane.
I/R-injury: Ischemia/reperfusion injury, referring to tissue damage caused by the restoration of blood flow following a period of ischemia or reduced blood supply.
Ischemia: Insufficient blood supply to tissues or organs, often leading to tissue hypoxia and cell damage or death.

Isoform: Variant form of a protein or RNA molecule encoded by the same gene, differing in sequence or splicing pattern, often exhibiting distinct functions.

J

JNK (c-Jun N-terminal Kinase): Subtype of MAPK activated by stress stimuli, regulating apoptosis, inflammation, and cell differentiation.

K

Kinase: Enzyme that catalyzes the transfer of phosphate groups from ATP to specific substrates, regulating their activity or function.
KO (knockout) mice: Genetically modified mice lacking a specific gene of interest, used to study the function and effects of the deleted gene.
Krebs Cycle: Metabolic pathway occurring in mitochondria, oxidizing acetyl-CoA to produce ATP, NADH, and FADH2 for oxidative phosphorylation.

L

Leptin: Hormone secreted by adipose tissue, regulating appetite, energy expenditure, and body weight by acting on the hypothalamus.
Ligand: A molecule that binds specifically to a receptor, enzyme, or other biomolecule, triggering a biological response.
Lipase: Enzyme released from the pancreas into the small intestine that breaks down lipids (fats) into glycerol and fatty acids, facilitating digestion and absorption.
Lipid: Organic compound insoluble in water, including fats, phospholipids, and steroids, serving as structural components of cell membranes and energy storage.
Lipid Bilayer: Double layer of phospholipid molecules forming the basic structure of cell membranes, regulating the passage of molecules and ions into and out of cells.
Lipid Peroxidation: The process in which reactive oxygen species (ROS) attack and degrade lipids in cell membranes, leading to cellular damage and dysfunction.
Lipoblast: Immature fat cell precursor, forming adipocytes in adipose tissue, contributing to fat storage and metabolism.
Lipopolysaccharide (LPS): Molecule found in the outer membrane of Gram-negative bacteria, acting as a potent immune stimulant and eliciting inflammatory responses.
Lipoxygenase: Enzyme responsible for the synthesis of leukotrienes and other lipid mediators from arachidonic acid, involved in inflammation and immune responses.
L-NAME (N-nitro-L-arginine methyl ester): Nitric oxide synthase inhibitor used in experimental studies to block the production of nitric oxide (NO) and study its physiological roles.
Long Term Depression: Persistent decrease in synaptic strength following low-frequency stimulation, involved in synaptic plasticity and memory processes.
Long Term Potentiation: Persistent increase in synaptic strength following high-frequency stimulation, thought to underlie learning and memory formation.

Lymph Node: Secondary lymphoid organ containing lymphocytes and immune cells, filtering lymph and facilitating immune responses to pathogens or antigens.

M

Macroautophagy: Type of autophagy involving the formation of autophagosomes to sequester cytoplasmic components for degradation.
Macrophage: Immune cell derived from monocytes, involved in phagocytosis, antigen presentation, inflammation, and tissue repair.
MAFbx: Muscle-specific E3 ubiquitin ligase involved in ubiquitin-mediated proteolysis and muscle atrophy.
Malondialdehyde (MDA): Reactive aldehyde produced as a byproduct of lipid peroxidation, commonly used as a marker of oxidative stress.
MAPK (Mitogen-Activated Protein Kinase): Protein kinase involved in signaling pathways regulating cell proliferation, differentiation, and survival.
Master Regulator: Key regulatory molecule or gene controlling the expression of multiple downstream genes or pathways, often critical for cell fate determination or developmental processes.
Matrix metalloproteinases (MMP): Family of enzymes involved in remodeling the extracellular matrix, regulating cell migration, tissue repair, and angiogenesis.
MCP-1 (Monocyte Chemoattractant Protein-1): Chemokine involved in the recruitment and activation of monocytes/macrophages during inflammation and immune response.
Mdx mice: Mouse model of Duchenne muscular dystrophy, characterized by a mutation in the dystrophin gene, resulting in muscle degeneration and weakness.
Mechanosensor: Cell membrane protein or ion channel that detects mechanical stimuli and converts them into intracellular signals, influencing cellular responses.
Mechanotransduction: Conversion of mechanical stimuli into cellular signals, regulating various physiological processes such as touch sensation, hearing, and muscle contraction.
Medical Nihilism: A philosophical skepticism or disbelief in the effectiveness or value of medical interventions or knowledge.
MEF2 (Myocyte Enhancer Factor 2): Transcription factor regulating muscle development, differentiation, and adaptive responses to exercise.
Memory Cells: Long-lived immune cells capable of recognizing and responding to specific antigens upon re-exposure, providing immunological memory.
Metabolism: Collective biochemical processes in organisms involving conversion of nutrients into energy and essential molecules for growth, maintenance, and function.
Methylation: Addition of methyl groups to DNA or histone proteins, regulating gene expression and chromatin structure.
Microbiome: Community of microorganisms (bacteria, fungi, viruses) residing in a particular environment, such as the human gut, skin, or soil.
Microglia: Resident immune cells of the central nervous system, involved in immune surveillance, inflammation, and synaptic remodeling.
Microvessel: Small blood vessel, including arterioles, venules, and capillaries, facilitating nutrient and oxygen exchange in tissues.

Mineral: Inorganic element essential for the proper functioning of enzymes, proteins, and other biological molecules in the body.
Mislocation: Abnormal or incorrect localization of cellular components, proteins, or organelles, contributing to cellular dysfunction or disease.
Mitochondria: Membrane-bound organelles responsible for generating ATP through aerobic respiration and regulating various metabolic processes in eukaryotic cells.
Mitochondrial Biogenesis: Process of generating new mitochondria within cells, regulated by signaling pathways in response to energy demands or metabolic stress.
Mitochondrial Fusion: Process by which individual mitochondria merge together to form a larger mitochondrial network, facilitating exchange of contents and DNA.
Monocyte: Type of white blood cell involved in innate immunity, differentiating into macrophages or dendritic cells and mediating phagocytosis and antigen presentation.
Morris water maze: Behavioral test used to assess spatial learning and memory in rodents by requiring them to find a submerged platform in a pool of opaque water using spatial cues.
Morphological: Pertaining to the form, structure, or shape of an organism, organ, or tissue.
Motor Neuron: Neuron that transmits signals from the central nervous system to muscle fibers, controlling muscle contraction and movement.
Motor Unit: Functional unit consisting of a motor neuron and the muscle fibers it innervates, controlling muscle contraction.
MRF4: Transcription factor belonging to the myogenic regulatory factors (MRFs), regulating myoblast proliferation and differentiation during muscle development.
mRNA (Messenger RNA): RNA molecule transcribed from DNA and serving as a template for protein synthesis, carrying the genetic information from the nucleus to the cytoplasm.
mTOR (mammalian Target Of Rapamycin): Serine/threonine protein kinase regulating cell growth, metabolism, and autophagy in response to nutrient and energy availability.
mTORC1-2 (mammalian Target Of Rapamycin Complex 1-2): Protein complexes containing mTOR kinase, regulating cell growth, protein synthesis, and metabolism.
MTT assay (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay): Laboratory technique used to measure cell viability and proliferation based on the metabolic reduction of MTT dye by living cells.
Multinucleate: Having multiple nuclei within a single cell, characteristic of certain cell types such as skeletal muscle fibers or some fungi.
Multivariate: Statistical analyses and models that involve multiple variables simultaneously, aiming to understand complex relationships among them.
Muscle RING Finger 1 (MuRF1): Muscle-specific E3 ubiquitin ligase involved in ubiquitin-mediated proteolysis and muscle atrophy.
Muscarinic Acetylcholine Receptors (mAChR): Mediate responses to acetylcholine, influencing diverse processes including neurotransmission, smooth muscle contraction, and glandular secretion.
Muscle Contraction: Process by which muscle fibers generate tension and exert force on bones or other tissues, resulting in movement or stabilization of body parts.
Muscle Progenitor Cell: Precursor cell involved in muscle development and repair, capable of differentiating into myoblasts and myocytes.

Myelin: Insulating sheath surrounding axons in the nervous system, facilitating faster propagation of action potentials.
Myelin Sheath: Lipid-rich membrane surrounding axons, formed by oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system.
Myoblast: Precursor cell involved in muscle development and repair, capable of differentiating into mature muscle cells (myocytes).
Myocyte: Muscle cell responsible for generating force and movement through contraction.
Myofiber: Single muscle cell composed of myofibrils and surrounded by endomysium, contributing to muscle contraction.
Myofibril: Contractile organelle within muscle cells composed of repeating sarcomere units, responsible for muscle contraction.
Myogenic Fusion: Process by which myoblasts fuse together to form multinucleated myotubes or muscle fibers during muscle development or repair.
Myoglobin: Oxygen-binding protein found in muscle cells, storing and releasing oxygen for aerobic metabolism during muscle contraction.
Myonuclei: Nuclei within muscle fibers responsible for regulating protein synthesis, repair, and adaptation in response to exercise or injury.
Myosin Heavy Chain: Protein component of myosin filaments in muscle cells, determining muscle fiber type and contractile properties.
Myostatin: Negative regulator of muscle growth and development, inhibiting the proliferation and differentiation of muscle cells, targeted in efforts to enhance muscle mass.
Myotube: Multinucleated muscle cell formed by the fusion of myoblasts during muscle development or regeneration.

N

NCAM: Neural Cell Adhesion Molecule, a protein involved in cell-to-cell adhesion, signaling, and neural development.
Nerve Impulse: Electrical signal transmitted along nerve fibers (neurons), propagating action potentials for communication between neurons or with effector cells.
NeuN: A neuron-specific nuclear protein used as a marker to identify and study neurons in brain tissue.
Neural Stem Cell: Multipotent cell capable of self-renewal and differentiation into various neural cell types, found in the central nervous system.
Neurite: Any projection from the cell body of a neuron, including axons and dendrites.
Neuroblastoma: Cancer arising from immature nerve cells, often occurring in children and originating in the adrenal glands or sympathetic nervous system.
Neuromuscular Junction: Synapse between a motor neuron and a muscle fiber, where neurotransmitter release triggers muscle contraction.
Neuromuscular Synapse: Synaptic connection between a motor neuron and a muscle fiber, mediating the transmission of nerve impulses and initiation of muscle contraction.
Neuronal Excitation: Process by which neurons generate action potentials in response to stimuli, leading to the transmission of electrical signals along nerve fibers.
Neuronal Inhibition: Process by which neurons reduce or suppress the generation of action potentials in response to inhibitory signals, regulating neural activity.

Neuropeptides: Small protein molecules acting as neurotransmitters or neuromodulators in the nervous system, regulating various physiological functions.
Neutrophil: Type of white blood cell involved in innate immunity, phagocytosing pathogens and releasing inflammatory mediators.
Neurotransmitter: Chemical substance released by neurons to transmit signals across synapses, influencing the activity of target cells.
Neurotrophic Factor: Growth factor promoting the survival, differentiation, and function of neurons, essential for neuronal development and maintenance.
Nicotinamide adenine dinucleotide (NADH): A coenzyme involved in cellular energy production, transferring electrons in metabolic reactions, particularly in glycolysis and the citric acid cycle.
Nicotinic Acetylcholine Receptor (nAChR): Ligand-gated ion channel receptor for acetylcholine, mediating fast synaptic transmission at neuromuscular junctions and in the central nervous system.
Nitric oxide (NO): A colorless, odorless gas molecule that acts as a signaling molecule in the body, regulating various physiological processes such as vasodilation, neurotransmission, and immune response.
Nitric oxide synthases (iNOS-eNOS-NOS): Enzymes that produce Nitric oxide from Arginine.
Nitrotyrosine: Biomarker of oxidative stress formed by the reaction of reactive nitrogen species with tyrosine residues in proteins.
NMDA Receptors: Ionotropic glutamate receptors involved in synaptic plasticity and memory formation, activated by the neurotransmitter glutamate.
Nociception: The physiological process of detecting and transmitting signals related to tissue damage or potential injury, leading to the sensation of pain.
Non-rapid eye movement sleep (NREM): A stage of sleep characterized by absence of rapid eye movements and slower brain waves.
Norepinephrine: Neurotransmitter and hormone involved in the body's stress response, regulating heart rate, blood pressure, and arousal.
Normoxia: Normal oxygen levels in tissues or organs, required for cellular respiration and metabolism.
Nuclear Factor erythroid 2-related factor 2 (Nrf-2): Transcription factor regulating the expression of antioxidant and detoxification genes in response to oxidative stress.
Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-kB): Transcription factor involved in immune response, inflammation, and cell survival.
Nucleotide: Basic building block of nucleic acids (DNA and RNA), composed of a sugar, phosphate group, and nitrogenous base.
Nucleus: Membrane-bound organelle containing the genetic material (DNA) of eukaryotic cells, regulating gene expression and cellular activities.
Nucleus Accumbens: Brain region part of the reward pathway, involved in motivation, pleasure, and addiction, particularly to drugs of abuse.
Null: Genetically engineered organism lacking a specific gene or gene function, used to study the role of the gene in development or disease.

O

Occipital lobe: Brain area primarily responsible for visual processing.
Oil Red-O staining: Histological technique used to visualize lipid droplets in tissues, staining neutral lipids such as triglycerides and cholesterol esters.
Oligodendrocyte: A type of glial cell in the central nervous system responsible for producing myelin, which insulates axons and facilitates efficient nerve signal transmission.
Ornithine decarboxylase: An enzyme that catalyzes the conversion of ornithine into putrescine, a key step in the biosynthesis of polyamines, essential molecules involved in cell growth, proliferation, and differentiation.
Oxidative Stress: Imbalance between the production of reactive oxygen species (ROS) and antioxidant defense mechanisms, leading to cellular damage.
Oxidization: Chemical reaction involving the loss of electrons or gain of oxygen atoms, often associated with oxidative stress and damage.
Oxytocin: Hormone and neurotransmitter involved in social bonding, childbirth, lactation, and maternal behavior.

P

p38: Subtype of MAPK activated by stress stimuli, regulating inflammation, apoptosis, and cellular responses to environmental stressors.
P70S6K: Protein kinase involved in the mTOR signaling pathway, regulating protein synthesis and cell growth in response to nutrient availability.
Paracrine: Signaling mechanism in which cells secrete signaling molecules (paracrine factors) that act locally on nearby cells.
Particulate Matter (PM2.5 / PM10): Fine or coarse solid particles and liquid droplets suspended in the air, categorized by size.
Parietal lobe: Brain area involved in processing sensory information, spatial perception, and integration of sensory and motor signals.
Pathogen-associated molecular patterns (PAMPs): Molecules derived from pathogens, such as bacteria, viruses, or fungi, that are recognized by the innate immune system through pattern recognition receptors (PRRs).
PAX7: Transcription factor expressed in muscle satellite cells, regulating their self-renewal and differentiation during muscle regeneration.
PCR (Polymerase Chain Reaction): Laboratory technique used to amplify specific DNA sequences through cycles of denaturation, annealing, and extension, enabling detection and analysis of DNA.
Peer-reviewed: The process in which scholarly work, such as research papers, is evaluated by experts in the same field before publication to ensure its quality, validity, and relevance.
Peptide: Short chain of amino acids linked by peptide bonds, serving various biological functions as hormones, neurotransmitters, or signaling molecules.
Pericyte: Contractile cell found in the walls of capillaries and small blood vessels, involved in regulating blood flow and vessel integrity.
Peroxisome proliferator-activated receptors (PPARs): Nuclear receptors regulating gene expression involved in metabolism, inflammation, and cellular differentiation.
Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α): A transcriptional coactivator regulating mitochondrial biogenesis and energy metabolism.

PGC1a (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha): Transcriptional coactivator involved in regulating mitochondrial biogenesis and metabolism.
pH: Measure of the acidity or alkalinity of a solution, determined by the concentration of hydrogen ions present.
Phagocytosis: Process by which cells engulf and internalize solid particles or pathogens, forming phagosomes for degradation and antigen processing.
Pharmacodynamics: Study of the biochemical and physiological effects of drugs on the body, including their mechanisms of action and dose-response relationships.
Pharmacokinetics: Study of the absorption, distribution, metabolism, and excretion of drugs in the body, determining their concentration-time profiles and bioavailability.
Phenotype: Observable characteristics or traits of an organism, resulting from interactions between genetic factors and environmental influences.
Phosphatase and tensin homolog (PTEN): Tumor suppressor protein regulating cell growth, survival, and metabolism by inhibiting the PI3K/Akt signaling pathway.
Phosphoinositide 3-Kinase (PI3K): Enzyme involved in cell signaling pathways regulating cell growth, survival, and metabolism.
Phospholipase-D: Enzyme catalyzing the hydrolysis of phospholipids to generate phosphatidic acid, involved in cell signaling and membrane remodeling.
Phosphorylation: Post-translational modification of proteins by adding a phosphate group, regulating protein activity, localization, and interactions.
Phylogenetic: Relating to the evolutionary history and relationships between organisms, often represented as phylogenetic trees based on genetic or morphological data.
Physoxia: Physiological oxygen levels in tissues or organs, optimal for cellular function and homeostasis.
Phytoncide: Volatile organic compounds emitted by plants with antimicrobial properties, thought to have health benefits when inhaled.
Pigment: Colored molecule or substance that absorbs and reflects specific wavelengths of light, giving tissues or structures their characteristic color.
Polysaccharide: Carbohydrate molecule composed of multiple sugar units linked together, serving as energy storage molecules (e.g., glycogen) or structural components (e.g., cellulose).
Postsynaptic: Refers to the region of a synapse, typically on the receiving end of a signal, where neurotransmitter receptors are located and where neurotransmitters bind to initiate a response in the receiving neuron.
PPARα (Peroxisome proliferator-activated receptor alpha): Nuclear receptor involved in fatty acid oxidation, lipid catabolism, and energy homeostasis, primarily in liver, heart, and skeletal muscle.
PPARy (Peroxisome proliferator-activated receptor gamma): Nuclear receptor involved in adipogenesis, lipid metabolism, and insulin sensitivity.
Presynaptic: Refers to the region of a synapse, typically on the transmitting end of a signal, where neurotransmitters are stored and released into the synaptic cleft to signal the postsynaptic neuron.
Programmed Cell Death: Cellular process regulated by specific signaling pathways, leading to controlled cell elimination, crucial for development and tissue homeostasis.

Proliferation: Process of cell division and increase in cell number, essential for growth, development, and tissue repair.
Promoter (Genetic): Regulatory region of DNA located upstream of a gene, controlling the initiation of transcription and gene expression.
Propionic Acid: Short-chain fatty acid produced by microbial fermentation in the gut, serving as an energy source and metabolic precursor, implicated in various health effects.
Protease: Enzyme released from the pancreas, mouth, & stomach that breaks down proteins into smaller peptides or amino acids, essential for various biological processes.
Proteasome: Cellular structure responsible for degrading and recycling proteins tagged with ubiquitin, maintaining protein homeostasis.
Protein Kinase B (AKT): Serine/threonine protein kinase involved in cell survival, growth, and metabolism, activated by growth factors and insulin signaling.
Protein Synthesis: Cellular process of translating genetic information from mRNA into functional proteins, involving transcription, translation, and post-translational modifications.
Proton: Positively charged subatomic particle found in the nucleus of atoms, contributing to the electrical potential across biological membranes and energy metabolism.
Proton leak: Leakage of protons across biological membranes, uncoupling the flow of protons from ATP synthesis in mitochondria, dissipating energy as heat.
Purines: Nitrogenous bases found in DNA and RNA, including adenine and guanine, and their derivatives such as ATP and GTP.
Pyroptosis: Form of programmed cell death characterized by inflammatory response and cell swelling, triggered by inflammasome activation.
Pyruvate: Three-carbon compound formed during glycolysis, serving as a substrate for the Krebs cycle or fermentation pathways.

Q

N/A

R

Radial arm water maze: Behavioral test used to assess spatial learning and memory in rodents by requiring them to navigate through a maze to find a hidden platform submerged in water.
Rapamycin: Macrolide antibiotic and immunosuppressant drug that inhibits the mTOR signaling pathway, used in research to study cell growth and metabolism.
Reactive Oxygen Species: Chemically reactive molecules containing oxygen, such as superoxide, hydrogen peroxide, and hydroxyl radical, involved in oxidative stress and signaling.
REM: Rapid Eye Movement, a stage of sleep characterized by vivid dreams and rapid eye movements, often associated with memory consolidation.
Retraction: Scientific term meaning the withdrawal or removal of a previously published research article, typically due to errors, ethical concerns, or misconduct discovered after publication.
RNA: Ribonucleic acid molecule involved in various cellular processes, including protein synthesis (mRNA), gene regulation (miRNA), and catalysis (ribozymes).

RT-PCR (Reverse Transcription Polymerase Chain Reaction): Variant of PCR used to amplify and quantify RNA molecules by first converting them into complementary DNA (cDNA) using reverse transcriptase.

S

SAMP8 mice: Accelerated aging mouse model commonly used in research on age-related cognitive decline and neurodegenerative diseases.
Satellite Cell: Quiescent stem cell located in skeletal muscle, activated during muscle injury or exercise to proliferate and differentiate into myoblasts for muscle repair.
Sarcoplasmic Reticulum: Specialized endoplasmic reticulum found in muscle cells, storing and releasing calcium ions for muscle contraction.
Sarcolemma: Cell membrane of muscle fibers, essential for excitation-contraction coupling and transmission of action potentials.
Sarcomere: Contractile unit of muscle composed of overlapping actin and myosin filaments, responsible for muscle contraction.
Second Messenger: Intracellular signaling molecule generated in response to activation of cell surface receptors, transmitting and amplifying extracellular signals.
Senescence: Biological process of aging or deterioration in cells, tissues, or organisms, characterized by reduced cellular function and increased vulnerability to stress and disease.
Serotonin: Neurotransmitter and neuromodulator involved in mood regulation, sleep-wake cycles, appetite, and other physiological processes.
SGK1 (Serum and Glucocorticoid-Regulated Kinase 1): Serine/threonine protein kinase regulated by growth factors and stress signals, involved in cell survival and ion transport.
SH-SY5Y cell: Human neuroblastoma cell line widely used in neuroscience research, modeling neuronal differentiation, function, and pathology.
Short Chain Fatty Acids (SCFAs): Organic acids typically composed of fewer than six carbon atoms, produced by the bacterial fermentation of dietary fibers in the colon.
Signal Transduction: Process by which extracellular signals are transmitted into the cell, leading to cellular responses or changes in gene expression.
Singlet Oxygen: Reactive oxygen species (ROS) formed by the excited state of molecular oxygen, capable of damaging cellular components.
siRNA (Small interfering RNA): Synthetic RNA molecule designed to target and silence specific genes by inducing degradation of complementary mRNA molecules.
Sleep spindle: Brief bursts of brain activity during stage 2 non-REM sleep, believed to play a role in memory consolidation.
Slow-wave sleep: A stage of deep sleep characterized by slow brain waves (delta waves), important for physical and mental restoration.
Smooth Muscle: Involuntary muscle tissue found in the walls of internal organs, responsible for peristalsis and regulating organ function.
SPECT Scan (Single Photon Emission Computed Tomography): Imaging technique used to visualize and measure radioisotope distribution in tissues, providing functional information about organ function or blood flow.
Splice: Process of removing introns and joining exons in pre-mRNA molecules during gene expression, generating mature mRNA transcripts.

Sprague-Dawley rat: Common strain of laboratory rat used in biomedical research for toxicology, pharmacology, and physiology studies.
STAT3 (Signal Transducer and Activator of Transcription 3): Transcription factor activated by cytokine signaling, regulating immune response, cell proliferation, and survival.
Substance P: Neuropeptide involved in pain perception and inflammation, released by sensory neurons in response to noxious stimuli.
Subunit (Receptor): Protein component of a receptor complex responsible for ligand binding and signal transduction.
Superfamily: A large group of related proteins or genes with similar structures or functions, often sharing evolutionary ancestry and biochemical characteristics.
Superoxide Dismutase (SOD): Enzyme that catalyzes the dismutation of superoxide radicals into oxygen and hydrogen peroxide, protecting cells from oxidative damage.
Swiss mice: Outbred strain of laboratory mice derived from a mixture of different strains, commonly used in pharmacology.
Synapsin 1: Neuronal phosphoprotein involved in regulating neurotransmitter release and synaptic vesicle trafficking.
Synaptogenesis: Process of forming new synapses between neurons, crucial for establishing neuronal circuits during development and synaptic plasticity.
Synaptic Cleft: Narrow gap between presynaptic and postsynaptic neurons, where neurotransmitters are released and bind to receptors, transmitting signals.
Synaptic Vesicles: Small membrane-bound organelles within presynaptic neurons, containing neurotransmitters that are released into the synaptic cleft.
Synapse: Junction between two neurons or between a neuron and an effector cell, mediating communication through neurotransmitter release and synaptic transmission.

T

T-Cells: Type of white blood cell involved in cell-mediated immunity, including helper T cells, cytotoxic T cells, and regulatory T cells.
Temporal lobe: Brain region associated with auditory processing, memory, emotion, and language comprehension.
Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL): A technique used to detect DNA fragmentation in apoptotic cells, indicating programmed cell death.
Terminal Half-Life: Time required for the concentration of a substance in the body to decrease by half during the elimination phase after reaching steady-state conditions.
Thiobarbituric acid reactive substance: Compound formed by the reaction of thiobarbituric acid with lipid peroxidation products, used as a marker of oxidative stress.
Time-under-tension (TUT): Training variable referring to the total duration a muscle is under strain during a set, coined by Charles Poliquin.
T-maze: Behavioral test used to assess spatial learning and memory in rodents by requiring them to choose between two arms of a maze to find a reward.
Toll Like Receptor: Pattern recognition receptor involved in innate immune response, recognizing pathogen-associated molecular patterns (PAMPs) and activating immune cells.

Transactivator: Protein that binds to DNA regulatory sequences and activates transcription of target genes, regulating gene expression.
Transcription: Process of synthesizing RNA molecules from DNA templates, mediated by RNA polymerase enzymes.
Transforming Growth Factor beta (TGF-b): A Cytokine involved in regulating cell growth, differentiation, and wound healing, with diverse effects on various cell types.
Trolox equivalent antioxidant capacity (TEAC): Measurement of antioxidant capacity that compares a substances' ability to neutralize free radicals with Trolox (vitamin E analog).
Tropomyosin: Protein associated with actin filaments in muscle cells, regulating muscle contraction by blocking myosin-binding sites on actin.
Tropomyosin receptor kinase A (TrkA): Receptor tyrosine kinase activated by nerve growth factor (NGF), regulating neuronal survival, growth, and differentiation.
Troponin: Regulatory protein complex associated with actin filaments in muscle cells, controlling the interaction between actin and myosin during muscle contraction.
TRPM8 (Transient Receptor Potential Melastatin 8): Ion channel activated by menthol and cold temperatures, involved in cold sensation and thermoregulation
TRPV1 (Transient Receptor Potential Vanilloid 1): Ion channel activated by various stimuli, including capsaicin (from chili peppers) and heat, involved in pain perception and thermoregulation.
Trypsin: Enzyme that breaks down proteins into smaller peptides by cleaving peptide bonds, found in the digestive system.
Tuberous sclerosis protein complex 1-2: Protein complexes containing TSC1 (hamartin) and TSC2 (tuberin), regulating the mTOR signaling pathway and cellular growth.

U

Ubiquitin ligases: Enzymes that attach ubiquitin molecules to proteins, marking them for degradation by the proteasome.
Ultra-performance liquid chromatography (UPLC): Advanced form of liquid chromatography with improved resolution, sensitivity, and speed, used for separating and analyzing complex mixtures.
Urea: A nitrogenous waste product formed in the liver from ammonia and excreted by the kidneys in urine.
UVB (Ultraviolet B): Type of ultraviolet radiation with wavelengths between 280 and 320 nanometers, capable of penetrating the skin and causing DNA damage.

V

Vasculogenesis: The formation of new blood vessels from precursor cells, typically during embryonic development or tissue regeneration.
VCAM-1 (Vascular Cell Adhesion Molecule-1): A cell surface protein involved in the early adhesion of leukocytes to endothelial cells during inflammation.
VEGF-A (Vascular Endothelial Growth Factor A): Growth factor promoting angiogenesis and vascular permeability, involved in wound healing, tissue repair, and tumor vascularization.

Ventricle (Heart): Hollow chamber of the heart responsible for pumping blood to the lungs (right ventricle) and the rest of the body (left ventricle).
Vitamin: Essential organic nutrient required in small amounts for various metabolic processes and physiological functions in the body.
Volatile Organic Compound (VOC): Organic chemical compound with high vapor pressure at room temperature, often emitted as gases from various sources including plants, pollutants, or metabolic processes.
Voltage-gated Calcium Channels (VGCCs): Transmembrane protein channels that open in response to changes in membrane potential, allowing calcium ions to enter cells.

W

Western Blot: Laboratory technique used to detect and quantify specific proteins in biological samples, based on protein separation by gel electrophoresis and detection using antibodies.
White fat: Energy-storing adipose tissue mainly storing lipids.
Wild-type mice: Mice that have not been genetically altered and serve as the control group in experiments involving genetically modified mice.
Wound scratch analysis: Assay used to study cell migration and wound healing in vitro, involving the creation of a cell-free area (scratch) in a monolayer of cells, followed by monitoring of cell migration into the wound area.

X

N/A

Y

YAP1 (Yes-associated protein 1): Transcriptional co-activator involved in the Hippo signaling pathway, regulating cell proliferation, survival, and organ size.
Y-maze: Behavioral test used to assess spatial working memory in rodents by measuring their spontaneous alternation between three arms of a maze.

Z

Zymogen: Inactive precursor form of an enzyme, requiring cleavage or modification for activation, often to prevent premature enzyme activity.

General Supplement Index

Acetic Acid: Pg. 556
Agmatine: Pg. 612
Alcohol: Pg. 466
Alpha-GPC: Pg. 662
Alpha-lipoic acid: Pg. 653
Alpha-Linolenic acid: Pg. 393
Ally-Isocyanate: Pg. 623
Ascorbic acid: Pg. 336 / 657
Aspirin: Pg. 308
B-Hydroxy-B-Methyl Butyrate (HMB): Pg. 306
B-Vitamins: Pg. 348
Bacillus Coagulans: Pg. 426
Barley Grass: Pg. 385
Beta-Alanine: Pg. 339 / 664 / 779
Beta-Carotene: Pg. 344
Betaine: Pg. 316
Betahydroxybutyrate: Pg. 431
Wild Blueberries: Pg. 325
Camellia Sinensis: Pg. 370
Capric acid / Caprylic acid: Pg. 394
Cannabidiol: Pg. 303
Chromium: Pg. 361
Coffee: Pg. 368
Conjugated Linoleic acid: Pg. 617
Copper: Pg. 437
Citric acid: Pg. 431
Creatine: Pg. 318
Dehydroepiandrosterone: Pg. 315 / 424
Docosahexaenoic acid / Eicosapentaenoic acid: Pg. 389
Echinacea: Pg. 425
Epigallocatechin Gallate: Pg. 326 / 643
GABA: Pg. 614 / 637
Gamma-Oryzanol: Pg. 628
Glutathione: Pg. 361
Glycine / Serine: Pg. 164 / 232 / 290 / 739 / 784
Hibiscus Sabdariffa: Pg. 317
Hydroxytyrosol: Pg. 313 / 948

Iodine: Pg. 335
Kombucha: Pg. 358
L-Arginine: Pg. 430
L-Aspartic acid: Pg. 436
L-Carnitine: Pg. 322
L-Citrulline: Pg. 429
L-Glutamine: Pg. 432
L-Histidine: Pg. 616
L-Ornithine: Pg. 346 / 441
Lactobacillus Rhamnosus: Pg. 427 / 510
Lactoferrin: Pg. 347
Lauric acid: Pg. 445 / 627
Lithium: Pg. 168 / 351
Lion's Mane: Pg. 313
Lutein: Pg. 335
Magnesium: Pg. 331
Melatonin: Pg. 354
Nicotine: Pg. 416
Oleuropein: Pg. 310
Piperine: Pg. 464 / 625
Potassium: Pg. 345
Quercetin: Pg. 299 / 657
Raspberry Ketone: Pg. 624
Rooibos: Pg. 356
Rutin: Pg. 307
Selenium: Pg. 351 / 641
Sildenafil: Pg. 427
Silymarin: Pg. 301
Sulforaphane: Pg. 358
Taurine: Pg. 435
THC: Pg. 480
Theaflavins: Pg. 371 / 664
Vitamin D3: Pg. 350
Vitamin E: Pg. 339
Vitamin K: Pg. 338
Yohimbine: Pg. 622
Zinc: Pg. 351 / 782

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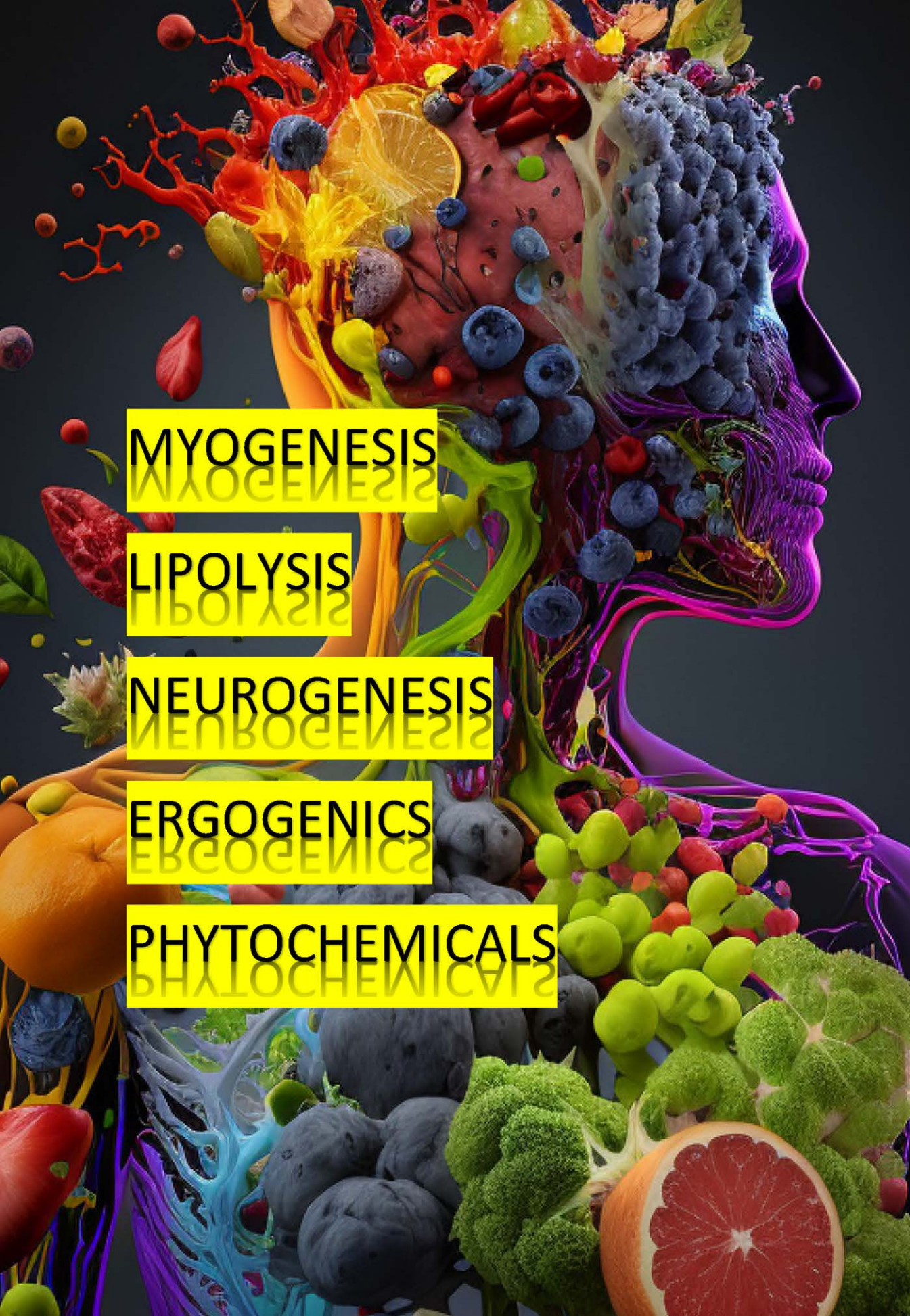
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LIPOLYSIS
NEUROGENESIS
ERGOGENICS
PHYTOCHEMICALS